

A DEVELOPMENTAL FACTOR IN SCHILDER'S DISEASE.

BY

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A clinico-anatomical study, from the developmental aspect, of three cases of subacute diffuse cerebral sclerosis, with a note about the demyelinating diseases generally, the developmental nervous disorders and the functional psychoses.

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1. INTRODUCTION.

INTRODUCTION.

In recent years increasing interest has been taken in the vulnerability of the growing individual to harmful influences acting at specific stages of development. It has already become clear that congenital structural anomalies, whether occurring naturally or in the course of animal experiments, arise as the result of an attack, at a critical moment of development, upon tissues in which profound growth activity is actually underway (Corner, 1944). Experimentally, it has been shown, also, by applying the knowledge that some vitamins form a part of the enzyme which control the metabolic activity of cells, that virtually all of the congenital anomalies which occur in man can be faithfully reproduced in animals by hypovitaminosis, particularly by hypovitaminosis-A (Woolam and Millen, 1956). Furthermore, the specially vulnerable phase of development of the bodily organs has been recognised to be the 'morphogenetic' phase, which embryologists distinguish from the later 'morphokinetic' phase, and which normally occurs during the early embryonic period. In the nervous system, on the other hand, morphogenesis has been recognised to be exceptionally prolonged and, in particular, in the cortical mantle of the human brain, is known to continue postnatally right up to full adult life (Kaes, 1907: Turner, 1948: Benda, 1952: Dodgson, 1954). It is understandable, therefore, that, while the most gross congenital structural anomalies of the nervous system undoubtedly/

undoubtedly have their origin in the earliest embryonic period, quite profound abnormalities, such as those associated with mongolism and certain forms of microcephaly, may arise later in the so-called 'neofœtal' period (Ballantyne, 1905) while others, such as infantile spastic diplegia, may arise in the foetal period proper (Brain, 1948) or at the time of birth (Benda, 1952) and that progressively more subtle anomalies of neurohistogenesis, affecting particularly the tissues of the cerebral hemispheres, may arise during infancy, childhood or adolescence.

The importance of certain specific factors in causing postnatal developmental nervous disorders is widely acknowledged. For example, the adverse effects of acute infectious and inflammatory disease upon the developing brain in infancy are well known while pathological studies of cases of trauma, according to Benda (1955), have demonstrated that the effects of a single head injury, particularly in infancy and childhood, may be to distort the whole of subsequent brain development. The condition of 'status marmoratus' has been attributed to myelinated axis cylinders growing diffusely throughout the putamen as a result either of birth injury or of postnatal infectious disease (Benda, 1952). It is accepted, also, that in kernicterus the bile staining is specially taken up by the neoencephalic caudate and lentiform nuclei which myelinate only after the 5th month of postnatal life (Adie and Critchley, 1927). The widespread cell degeneration of dementia infantilis (Heller's disease) has/

has been attributed to post infectious, degenerative or metabolic causes, while in childhood encephalitis lethargica the effects upon mental development, especially in the sphere of character, have been universally recognised. Over 60 years ago Vulpius (1892) claimed to show that general malnutrition in childhood and adolescence retarded the development of those tangential fibres of the cortex which he had proved to be still developing in normal subjects at the age of 17. It is now becoming clear that the undoubted dependence of the human infant upon emotional nourishment as much as upon milk and food has a comparable significance for the problem of cortical maturation during infancy and childhood, because psychoanalytic findings generally, and recent ethological research into such phenomena as 'imprinting', indicate that environmental influences play an essential role in the progressive structural organisation of the growing postnatal cortex. Now, the role of psychological factors in developmental nervous disorders is not fully understood but Bourne (1955) claimed to be able to recognise clinically a specific form of mental defect, 'protophrenia', which he felt was attributable to defective 'mothering' in early postnatal life and which accounted for as much as 10% of extreme deficiency. Bowlby (1951), who made fundamental contributions in this field, and rightly described the study of the embryology of the personality during early life as 'a field rich and ripe for research', pointed out that the electroencephalographic tracings of aggressive psychopathic/

psychopathic adolescents were strikingly similar to those of normal children aged three to five and suggested that this fixation at an earlier level of functioning might prove to be psychogenic in origin. Also, in his account of the lasting effects of maternal deprivation on the human infant, while he emphasised the importance of factors which are usually and perhaps more naturally described in psychological terms, at the same time he hinted that the elucidation of the neurophysiological basis of these processes might not be far distant.

Nevertheless, as Leigh (1955) pointed out, the late maturational processes in the brain, and the individual cytoarchitectonic variations associated therewith, have hardly been investigated in their relation to disease. In a very large group of developmental nervous disorders it is, in particular, extremely difficult to assess even the relative importance of physical and psychological factors. For example, the psychogenic origin of nocturnal enuresis is clear enough in many cases while, in others, certain features suggest that an important factor is delay in the maturation of certain nervous tracts and centres. The developmental speech disorders, when preceded or accompanied by the feature described as 'extreme autistic aloneness' are now commonly diagnosed as 'early infantile autism' the establishment of which, by Kanner (1943), was characterised, by Benda (1952), as a fundamental contribution to child psychiatry. Such autistic children are at first suspected to be severely feeble minded and make no anticipatory posture preparations to/

to being picked up - a behavioural pattern which should mature, according to Gesell (1948), at the 4th month. They are subsequently thought to be deaf, or word-deaf, and are often mute and indeed the relationship of this syndrome to the developmental speech delays would seem to be very close especially in view of the fact that thirteen of Kanner's twenty patients acquired speech in due course. The developmental agnosias, apraxias, aphasias, dysarthrias and dyslexias, with their secondary psychoneurotic or delinquent complications, have been well known for a long time (Orton, 1925; 1937; Worster-Drought and Allen, 1928; Travis, 1931) and their importance has been stressed again by Morley, Court, Miller and Garside (1955). The analogous condition of specific developmental dyslexia appearing at school age in otherwise healthy and intelligent children is of importance again because of the possible neurotic or delinquent complications. Under the heading of 'motor aphasia', it was attributed bluntly by Kanner (1935, 1948) to emotional conflict and Mildred Creak (1954) took a similar view although as 'congenital alexia', this condition was recognised long ago by Oppenheim (1911) and others and Hinshelwood (1917), the Glasgow ophthalmologist believed that these cases were due to congenital defects in the angular gyrus. Orton (1925, 1937) concluded that they were due not to an organic 'lesion', however, but to a deviation, during development, in the process of establishing unilateral dominance in individual cortical areas. Schilder (1944), agreeing with Orton's views so far as/

as they went, emphasised the fact that it was from the neurological point of view that congenital reading disabilities could and must be interpreted and that they were probably due to variable development of those parts of the brain which were indispensable to the function of reading. Hallgren (1950) found the incidence of the condition to be as high as 10% and that there was no association with certain specified and commonly invoked environmental factors. Ettlinger and Jackson (1955) thought that there was probably some hereditary factor in this condition which governed cortical maturation of function and the proper establishment of cerebral dominance. Of greater importance than the problem of these developmental nervous disorders is the problem of the aetiology of those so-called functional psychoses which appear for the first time during the period of life when the brain is not fully mature. The psychogenic origin in early childhood of these psychoses - particularly schizophrenia and manic depressive psychosis - has of course long been a familiar, if unproved, concept while actual psychosis in children is increasingly recognised clinically (McHarg, 1954). Furthermore, experience with the psychotomimetic drugs and with the pharmacological treatment of the functional psychoses in adult life suggests that histochemical abnormalities in the brain characterise the full development of these conditions and indicates that in this field it has now become essential to give much greater attention to such structural-functional deviations in the histogenesis of/

of the areas of the human cortex of late phylogenetic and ontogenetic development and to the histochemical abnormalities which may stem from these.

The greatest difficulty in approaching the problem of the aetiology of the developmental nervous disorders lies in lack of basic knowledge about the histological, biochemical, functional and ethological aspects of postnatal cerebral development. The monumental work of Conel (1939, et seq.) on the postnatal histogenesis of the cortex is an important first step in remedying this deficiency and further developmental studies by means of electronmicroscopy (c.f. Wyburn, 1958) may eventually advance this work especially in association with researches on behavioural development. However, Conel's work did not extend to a study of the white matter and it is curious that this important aspect has been almost completely ignored. A comparable difficulty lies in the fact that the direct neuropathological investigation of the developmental nervous disorders, even with improved modern techniques, will almost inevitably be held up because the patients who suffer from them rarely come to autopsy. At the present time the most profitable approach to a more adequate understanding of these conditions will perhaps lie in more detailed clinical and neuropathological studies than in the past of those more serious and progressive diseases of the actively maturing brain in which the ultimately fatal morbid process seems to act diffusely, to develop insidiously and, in the rate of its progress, to be commensurate in some sense with the concurrent/

concurrent histogenetic processes it opposes. Predominantly clinical studies of such conditions would depend for any special value in this respect largely upon careful observation of the earliest symptoms at different ages of onset because these would be the most likely to throw light upon the site of the greatest vulnerability of cerebral tissues. Moreover, as the earliest symptoms would often be of a predominantly psychological nature, it would be anticipated that clinical studies having such a special value would come mainly from psychiatric sources. The subacute form of diffuse sclerosis of the brain, occurring at widely different ages, would seem, on a priori grounds, to be eminently suitable for such an enquiry and it was, in fact, the unusually early recognition of three such cases which prompted the present clinico-anatomical enquiry.

The first two of the cases studied were referred to a psychiatric clinic at a stage when symptoms of brain dysfunction at a purely 'psychological' level were the only features. In the first of these, an adolescent, it was the striking similarity of the clinical picture to that of the hebephrenic form of schizophrenia which was of special interest because diffuse sclerosis was not suspected until shortly before death. In the second case, that of a young schoolboy, particularly detailed clinical records of the psychiatric findings were embarked upon at an early stage because the implications of the initial symptom of difficulty in learning to read were appreciated in relation to the problem of 'developmental dyslexia' and because the diagnosis of 'Schilder's disease' was/

was suspected even at that stage. In both of these cases, with the co-operation of relatives and school teachers, it was possible to assess even the onset of those elusive early mental symptoms which were directly observed at the first psychiatric interviews, while the subsequent ingravescence of these symptoms was personally studied up to the stage when objective physical signs of organic nervous disease began to appear. Subsequently, in these two cases and in the third case (an infant, who was also studied from a comparatively early stage), the progress of the disease was followed clinically through the well known stages of obvious physical signs leading up to the fatal termination which made neuropathological and anatomical studies possible. It is of interest to note that the clinical suspicion of diffuse sclerosis in the adolescent was, at first, unconfirmed pathologically. In the case of the second patient, the young schoolboy, after the clinical diagnosis had been confirmed pathologically, wedges of the cortex from a large number of different areas, selected to correspond as closely as possible to Flechsig's myelinogenetic zones, were removed with the intention of studying, topographically and comparatively, the involvement of the subjacent white matter. It was in view of the interesting features of this case that reassessment of the histological sections in the first case was requested by the author and kindly carried out, a year after the original autopsy, by Dr. A. T. Sandison, of the Pathology Department of the Western Infirmary, Glasgow. It was only then that the clinical diagnosis was confirmed./

and confirmed, / comparative studies of the myelinogenetic zones were unfortunately not possible owing to the fact that the whole brain was no longer available. The third brain, that of the infant, was subjected to a topographic: ally more detailed study including an attempt to correlate, more accurately, the sections taken, with Flechsig's myelinogenetic zones.

In the following account of this investigation, which is put forward as a contribution to the general problem of the developmental nervous disorders the functional psychoses and the demyelinating diseases , present knowledge of the relevant aspects of the normal growth and development of the cerebral hemispheres, and particularly of the so-called 'association areas', during infancy, childhood and adolescence will be outlined as it is this late growth which must form the developmental background against which such cases are to be studied. Special attention will be given to the maturation of the gliovascular element, particularly of the interfascicular oligodendroglia, and its myelinogenetic function in the white matter - the topographical aspects of which will be tentatively related to the functional maturation of the brain and to the behavioural maturation of the individual which this subserves. The full clinical and morbid-anatomical, accounts of the three cases will then be recorded - but, for convenience, in order of age rather than in the order in which they were observed. After this, there will be a discussion of the relevance of the developmental myelinogenetic background for the pathogenesis/

pathogenesis of diffuse sclerosis. In this discussion there will first of all be a survey of the historical aspect of the developmental approach. This will be followed by an account of the clinical aspects with special reference to the sequence of neuropsychiatric symptom-development in the earliest stages of the disease.

Then there will be a brief account of the pathology of the condition with special reference, once more, to the onset and mode of spread of the initial focus. A general discussion of the aetiological and pathogenetic factors will follow with special reference to the role of a developmental vulnerability of the white matter in predetermining the variable site of onset of the demyelinating process at different ages. Finally, there will be a brief note about possible analogous developmental tissue factors in the developmental nervous disorders, in the functional psychoses and in the other demyelinating diseases - especially multiple sclerosis and the concentric sclerosis of Baló.

SOME RELEVANT ASPECTS OF POSTNATAL BRAIN GROWTH

Diffuse sclerosis in man, unlike 'swayback' in lambs, normally begins during postnatal life. Three cases of 'congenital' demyelinating neuropathy were, however, described by Mackay (1940) and a diffuse demyelinating condition, apparently arising prenatally and thus resembling 'swayback' in lambs, was described by Winkelman & Moore (1942). The prenatal growth of the human brain, which would form the background for a developmental study of such cases, has been well investigated and described, particularly so far as cerebral cytoarchitectonics is concerned (Alderson, 1950), and will not be discussed further here. Attention will be devoted, rather, to the developmental changes which take place in the brain during postnatal life.

2. SOME RELEVANT ASPECTS OF POSTNATAL BRAIN GROWTH.

Gross morphological aspects.

The postnatal growth of the brain is widely known and recognized to be considerable during early infancy, but not always to be appreciable even during childhood and adolescence although Solomon and Dunn (1922) found that the increase in size of the brain which occurred after the age of 5 amounted to as much as 15%. It has also been said that this late postnatal growth continues until the 17th or 18th year of life (Gray's Anatomy, 1950) or even until the age of about 25 years (Bailey and von Bonin, 1951). Late brain growth is dependent upon expansion both of the cortex and of the underlying cerebral white matter and particularly upon the maturation of the glial component in the function of building up the myelin sheaths of the nerve fibres.

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Kaes (1907) described, with an accompanying atlas, the late gross developmental changes in the cortex and traced them into the 5th decade. He found that cortical thickness in the adult was less than it had been in the first month of life, that progressive thinning was particularly rapid between the third month and the end of the third year, that this process continued, more slowly, until the end of the 20th year and that after this age the cortical thickness began to increase - reaching its maximum in the 5th decade when, once more, a decrease set in. Dividing the cerebral cortex into an inner and an outer principle layer ('Hauptschicht') Kaes also found that the thickness of the inner principle layer increased steadily from birth up to the 5th decade but that the alterations in the thickness of the outer principle layer corresponded to the complex changes already described for the cortex as a whole. He found that these changes in thickness showed considerable local variations and that maximal cortical development was reached in different regions at different ages. Kaes believed that the external principle layer played a special role in the development of the individual, particularly of the higher mental life, because ~~of~~ its special manner of development continued into the fifth decade. He believed also that the regions of the cortex which were more richly supplied with nerve fibres were the narrower parts. These late developmental changes in the cerebral cortex were further discussed by Economo and Koskinas (1925), who, although they/

they called in question the accuracy of some of the original measurements made by Kaes, reproduced several of his diagrams and summarised his findings in considerable detail, pointing out that, if confirmed, they would be of fundamental importance.

Now, postnatal cortical growth is not a matter of steady, generalised, expansion but, on the contrary, is an uneven process consisting of a series of spurts of activity in different regions, a fact upon which the altering pattern of gyri and sulci traceable during development depends. Indeed the growth process seems to be largely concentrated, after the period of infancy, in those so-called 'association areas' whose special importance lies in the fact, that they are peculiar to man and of late phylogenetic development. Light was shed by Turner (1948) upon the topographical variations in the rate of postnatal cortical growth, by a painstaking study of a series of human brains up to the age of twenty years, in which he followed the development of the gross cerebral cortical pattern of gyri and sulci. He distinguished between the 'early post-uterine', and the 'late post-uterine', stages of this development and, in describing his observations on the latter period, between the age of 2 and adult life, Turner drew particular attention to the changes taking place in the parietal, temporal and frontal regions. He found that in the parietal region the exaggeration of the supra-marginal, angular and post-parietal gyri which had earlier been taking place was intensified but that the greater part of parietal growth, though not all, was attained at the age/

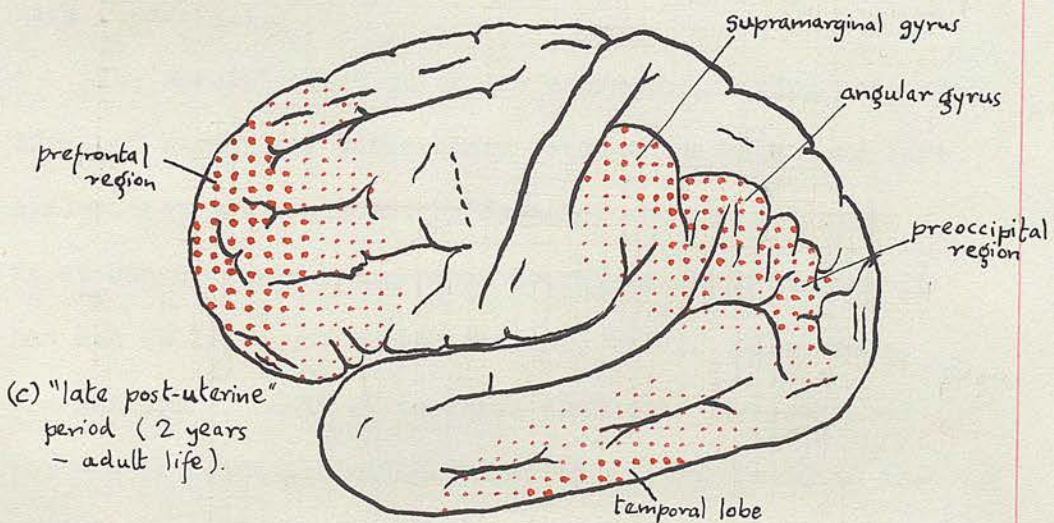
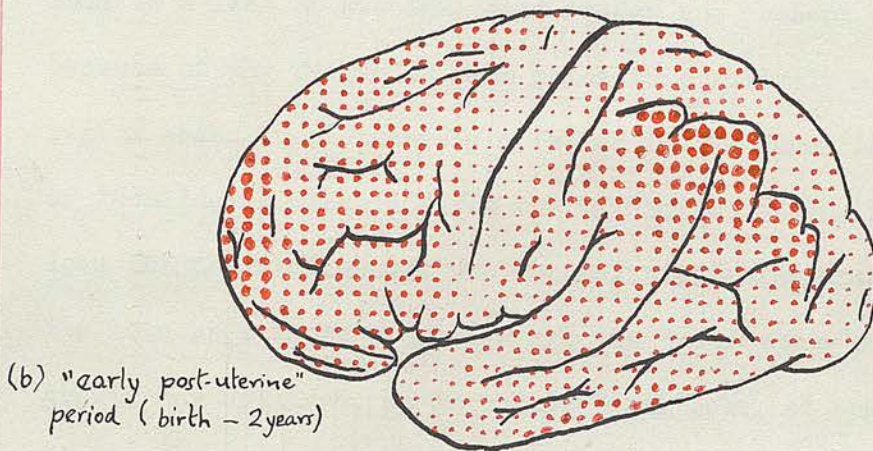
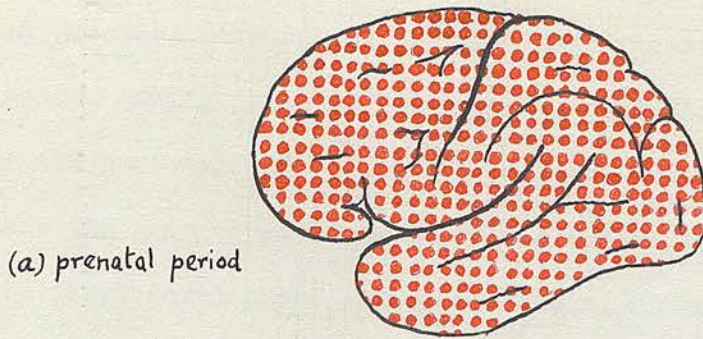


Fig. 1. Diagram (after Turner) to show the development of gyri and sulci in the postnatal brain. Stippling indicates intensity of growth activity.

age of 5 and the "submaximum" at the age of 10. In the temporal lobe, the changes were due to posterior expansion, the greatest development and most significant growth changes taking place in close spatial relationship to changes in the parietal and occipital regions. Indeed, he found that the preoccipital region of the cortex was late in its final development and that changes, minor in degree, continued in this region even in early full adult life. This is a fact of special interest for the present study because of the frequency with which this actively maturing region seems to be severely affected in the juvenile forms of 'Schilder's disease'. In the maturation of the frontal lobe the notable feature was the relative enlargement of the lobe as a whole and, although the "submaximum", of growth was attained, as in the parietal lobe, at the age of ten, the process of expansion continued here, in its distinctively diffuse way, practically through to adult life (see Fig.1)

The special question of the emergence, during postnatal life, of structural differences between the right and left hemispheres was mentioned by Economo, who characterized it as one of several important questions which he himself had had to leave untouched (Stengel, 1930). Since then, the structural basis of cerebral dominance has continued to receive scant attention. Kaes (ibid) had found in the adult that the left cortex was, usually, narrower than that of the right and considered also that cortical narrowness betokened higher development and for this reason functional

functional dominance has been supposed, by some, to depend upon the dominant hemisphere maturing, structurally, in advance of the non-dominant.

Cytoarchitectonic aspects.

The macroscopical changes in the developing cerebral hemispheres postnatally are intimately dependent, of course, upon underlying microscopical changes and, while it is known that from the purely neuronal aspect the definitive cytoarchitectonic pattern of the cerebral cortex is established in the normal full term infant at the time of birth and that no new nerve cells are added thereafter, neuronal changes continue to take place postnatally. These mostly involve the cell processes and take the form of axonal growth, increased dendritic arborization and the formation of new connections as a result of which the cell bodies become progressively less densely packed together. Aldama (1930), comparing histologically the brains of two children aged one and five years old respectively, was thus able to show that the cortex of the older of the two had a lesser cell density than that of the younger but that this cell density, nevertheless, still remained greater than that in the average adult. In this way he confirmed that further important developments in the cortex continued to take place after the age of five.

Gonell, (1939, 1941, 1947, 1951), pointed out that it was these intercellular changes which, no doubt, explained the fact that the infant's brain, as it grew, became much less

less soft and gelatinous in its consistency than it was at birth. His monumentally detailed histological study of the postnatal development of the normal human cerebral cortex was instituted in a projected attempt to correlate these changes with the development of behaviour in the normal child and they represented a logical extension of that of Economo who had repeatedly stressed that his own work on the cytoarchitectonics of the brain was not meant to represent a final static picture but rather to serve as a foundation for wider researches (Stengel, *ibid*). Conel, in studying the degree of structural maturity in different cortical areas at different ages, used nine criteria of developmental differentiation. They were (1) the width of the cortex (2) the number of nerve cells (3) the size of the nerve cells (4) the condition of the chromophil substance (5) the neurofibrils (6) the size, length and compactness of axons and dendrites (7) the pendunculated bulbs (8) the size and quantity of exogenous fibres (9) the stage of myelination. He confirmed that in the postnatal period of life the various neocortical areas developed at different times and that the relative degree of differentiation of the nerve cells and their processes, (features which were taken as an index of tissue maturity) varied consistently from area to area according to the age of the brain examined. He also showed that neuronal elements within each cortical area had a developmental sequence of their own, the deeper layers and the larger cells maturing earlier. As a result of his studies he confirmed that there were definite foci of maturation in/

in the cortex from which the process spread horizontally as the child developed. Consequently, in moving away from these primordial centres, there was normally to be found a graded decrease in structural differentiation of the neurones. Developmental changes in the cortical nerve fibres during childhood and adolescence have been known for a long time for it had been shown, by Vulpinus (1892), that the development of the tangential fibres in certain regions of the cortex was still taking place even at the seventeenth year. Kaes (ibid) in determining the number of projection bundles per millimetre breadth of the cortex at various ages had found that the maximum was attained about the 20th year of life, a finding in which there were, however, regional variations, the maximum being attained at different ages in different regions.

Now, it is the structural maturation of the cortical areas of late postnatal development which is of special relevance for the present enquiry but unfortunately this is a subject which has, with a few exceptions, received little detailed attention. Stengel (1930) made morphological and cytoarchitectonic studies in several brains in both normal and deaf and dumb subjects of the building up ('Bau') of the inferior frontal gyrus (Broca's area) a region upon which the complete functional maturation of motor speech depends and which, as Bailey and von Bonin (1951) pointed out, is a characteristically human zone and nowhere belongs to the anthropoid apes. Aranovich (1939) and De Leonardis (1948) who studied the same area, demonstrated an increase in cell size paralleled by/

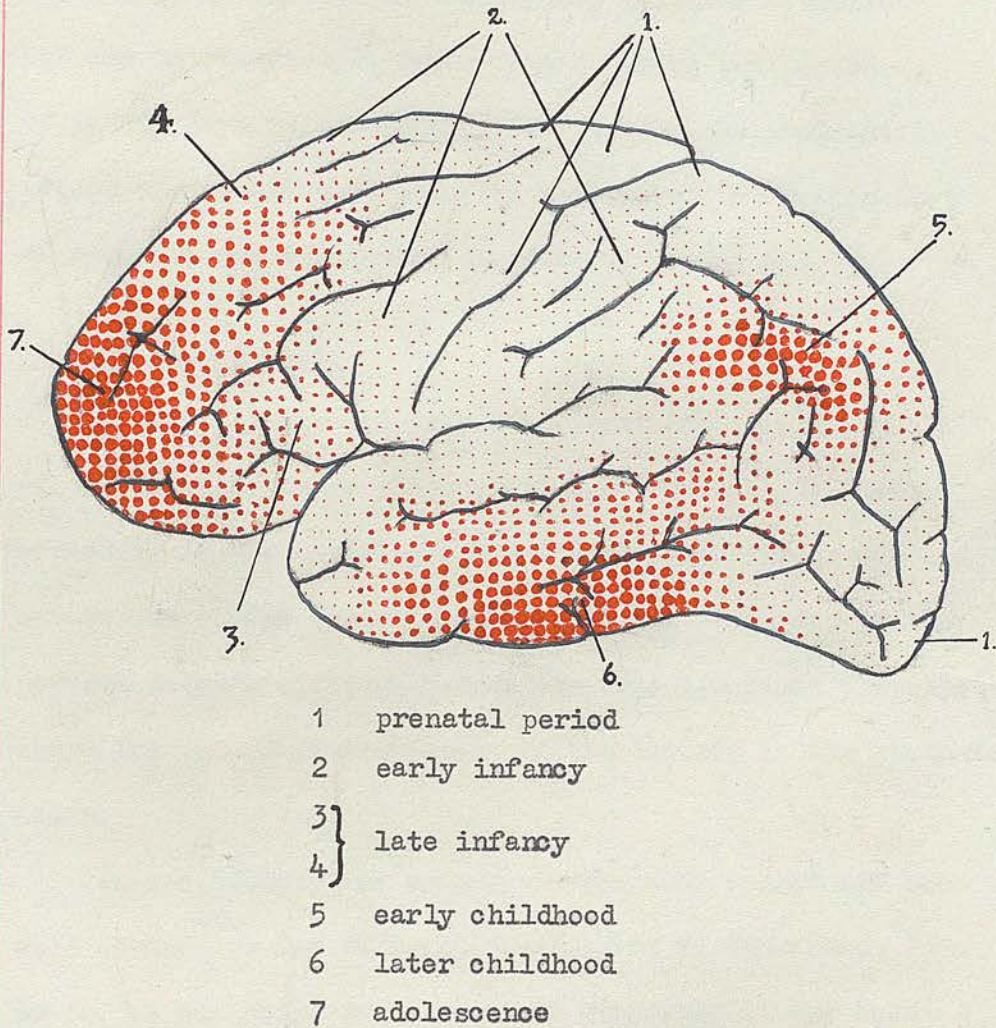


Fig. 2. Diagram (after C. and O. Vogt, but with their stippling reversed to emphasise the regions of late development) to show tentative times of maturation in different areas .

by a decrease in cell density. The findings of all these authors consistently indicated that the structural maturation of the inferior frontal gyrus continues until the age of three. The cytoarchitectonic maturation of the parietal and inferior temporal association areas does not seem to have received any comparably detailed attention but may be presumed to occur later, during the period of school days (vide Turner, 1948), while the prefrontal region presumably undergoes its structural maturation last of all with the attainment of adult life (see Fig.2).

Gliovascular aspects.

Closely integrated with the growth and maturation of the nerve cells of the cortex, and especially of their processes in the underlying white matter, is the growth and maturation of the associated gliovascular component of the nervous tissues although almost complete ignorance prevails about the late differentiation of the latter in the postnatal brain.

In particular, the mesodermic-vascular aspect has been ^{only} well studied, so far as early development is concerned. So far as postnatal development is concerned it has been approached, only indirectly and inferentially - e.g. by Doust (1955) and Doust and Salna (1955), following work by Olkon (1939) and Hauptmann and Myerson (1948); in studies of capillary structure in the skin in a large number of subjects. These authors found that many of the capillary forms observed resembled intermediate forms in the normal developmental series and they noticed, in certain subjects, the presence of constitutionally arrested and deviated capillary/

deviated capillary development amounting even to gross abnormalities of the vasculature and of its more minute extensions. It is particularly interesting to note that these authors found firm correlations between specific categories of abnormal capillary differentiation and the occurrence of specific forms of mental dysfunction.

The microglia, which is also of mesodermic origin, appears comparatively late in intrauterine life and, according to Penfield (1928), microgliocytes enter the myelinating tracts at the time of the onset of myelination by 'fountains' located in three areas of the brain where the pia comes into close contact with the white matter. They spread rapidly from these 'fountains' along the clefts in the white matter by means of amoeboid movements. The first description of microglial cells was attributed, by Glees (1955), to Ford Robertson (1899), whose platinum method gave a more exact picture than did the methods of other subsequent writers (e.g. Nissl's). Glees, who considered it surprising that Ford Robertson's discovery was not at all generally accepted, put this neglect down partly to the fact that Nissl's school had more adherents and partly to the subsequent strong influence of the Spanish school. He suggested, however, that it would be appropriate to refer to microglial cells, the 'Hortegazellen' of the German literature, as 'Robertson-Hortega' cells so that the part played by the Edinburgh pathologist in their discovery and description would not be overlooked. Ford Robertson had at first considered these cells to be ectodermal in origin but in later years (1900a, 1900b) had changed his opinion. It is interesting/

interesting to note that the controversy over their origin continues and recent work has suggested the possibility that, after all, these cells may have an ectodermal origin, as was originally believed by Ford Robertson. Indeed, Farquhar and Hartmann (1957), by means of electron microscopy, found many cell forms, even in normal nervous tissue, which seemed to be transitional between microglia and other glial cell types and they suggested a previously unsuspected capacity of these cells to differentiate into other glial cell types. Microgliocytes, which, in myelin metabolism, seem to be mainly concerned with the katabolic aspects, give rise, in disease, to the 'compound granular corpuscles'.

The ectodermal macroglia has been studied in its early development by many workers and Glees (1955), in his comprehensive monograph, summarised previous work and included his own important contribution. In particular, the active part played by the macroglia in the early prenatal stages of developing nervous tissue has received special attention from Hess (1955) who investigated the time at which the ground substance of the central nervous system appeared during foetal development and suggested that the astrocytes which appeared about the 3rd foetal month could elaborate part of this and thus provide the colloidal substrate for orientation of the growing nerve fibres. His work therefore suggested the direct importance of astrocytic development for the axonal differentiation of neurones and Lumsden's (1955) observation that the tips of the cell process of normal adult astrocytes were pseudopodic and slow moving, and that some had the appearance, also, of being secretors, may be/

be interpreted as further evidence tending to confirm this suggestion. The early development of astroglia and oligodendroglia in the optic nerves was studied by Lundberg (1939) who said that the stream of small cells arising from the ectoderm and forming the ocular penduncle constituted the matrix from which the neuroglia was built up. Following centripetal penetration of the nerve fibres, these small cells appeared at first to be still undifferentiated and to place themselves without any detectable order or relationship the one to the other but, later, two types of cell, bearing resemblances to astrocytes and oligodendrocytes respectively, became differentiated.

The macroglial aspects of late gliovascular differentiation in postnatal life have, on the other hand, scarcely been approached. Farquhar and Hartmann (1957) pointed out that even in recent direct electron-microscope developmental studies attention had been largely confined to neuronal and vascular elements and that the ectodermal glial component, particularly that of the white matter, had been largely neglected. They themselves, however, investigated, by this means, neuroglial structures in their relationship to the neuronal and vascular components. Kryspin-Exner (1943) grouped regions of nervous tissue having similar types of glia and, more recently (1952), carried out differential counts of astroglia, oligodendroglia and microglia in varied sections, while Friede (1953) raised once more the question of the practical value of the 'glia index' (ratio of glial cells to neurones) in a variety of clinical conditions. Despite great ignorance about the late/

late maturation of the gliovascular element in the brain, it seems to be established (Gerard, 1955), however, that one of the major functions of mature glia is to stabilize the composition of the intercellular fluid and the internal environment in which the neurone functions. Furthermore, the formation and nutrition of the myelin sheath seems to be a special aspect of this general function so that it may be that the important bearing which maturation of the gliovascular element has upon the final structural-functional ripening of the nervous system as a whole is by virtue, par excellence, of the part it plays in the final stages of the maturation of the myelin sheath.

It has, of course, been believed for many years that neuroglia played an important part in forming and maintaining the myelin sheath. For example, Boll (1869) attributed the source of myelin in the chick embryo to fat granular cells, Jastrowitz (1871) associated the widespread diffusion of fat in neuroglial cells with myelin deposition and Wlassak (1898) believed that myelin accumulated in the blood and was then transported, by glial cells, from the blood vessels to the nerve sheaths in the form of minute globules. Nowadays, the glial element which is believed to be mainly involved in the anabolic aspects of myelin metabolism is the oligodendroglia, the cells of which are the analogues of the Schwann cells in the peripheral nervous system. Because of its special significance for the demyelinating diseases, the oligodendroglial component of the gliovascular element calls, now, for/

for more detailed discussion.

Oligodendroglial aspects.

Clayton (1932), whose work was confirmed by Hilton (1943), reported that oligodendroglia was absent in the invertebrates, appeared late in the phylogenetic scale of development and was only present where the formation and maintenance of myelin was required. Comparative studies of oligodendroglia as between cold and warm-blooded vertebrates, carried out mainly by Italian workers, have suggested that, ascending the phylogenetic scale, oligodendroglia assumes progressively greater importance. Walsh (1957) pointed out that it was the development of the myelin sheath which opened the way for the evolution of animals with highly developed sense organs, for it became practicable to use many fibres having rapid velocities of conduction. Furthermore, within the group of the warm-blooded vertebrates, comparative morphological and histochemical studies of gliovascular structures in birds and mammals have demonstrated certain differences in glial cells notably and significantly in those of the telencephalon - those in other parts of the nervous system showing no such differences (Bairati and Bartoli, 1955). In the human brain, oligodendroglia comprises by far the most numerous group of cells after nerve cells and, its efficient maturation being perhaps a prerequisite for normal adult mental processes, it may well assume, here, paramount functional importance also.

According to Glees (1955), oligodendrocytes were originally thought to be adendritic i.e. to be cells having/

having no processes and Andrew and Ashworth (1945) indeed described a group of truly adendroglial cells which, they felt, deserved a name of their own. However, the first description of true oligodendroglial cells is attributable, according to Penfield, to Ford Robertson (1897) who by means of his platinum stain demonstrated the characteristic: ally few protoplasmic expansions. It was Hortega (1921) who established that these cells had a few dendritic processes and who first introduced the term 'oligodendrocyte'. Penfield (1924, 1930), using improved staining methods, showed that the cells had rather more processes than Hortega had described and it was the confirmation of Hortega's work by Penfield, with his even fuller account of the oligo: dendrocytes, which no doubt accounts for Greenfield's (1933) statement that the first English description of these cells had appeared in Penfield's paper although Penfield had himself insisted on Ford Robertson's primacy in this field and had explained how Cajal had misunderstood Ford Robertson's work as a result of knowing it not in the original but only at second hand through a paper in Italian by Cerletti. When confirming Hortega's detailed description of oligodendrocytes (which apparently Cajal had been unable to do) Penfield had re-examined an original histological preparation made by Ford Robertson and had satisfied himself that the cells, which Ford Robertson had originally been able to stain and describe, had been the same cells as those described by Hortega years later. He pointed out that Hortega (Cajal's pupil) had in fact rediscovered this cell and had undoubtedly provided a fuller description and demonstration of it than had been possible to/

to Ford Robertson. Despite the considerable neglect in the English, German and Spanish literature of Ford Robertson's pioneer work in this field it is interesting to note that it seems always to have been well known and acknowledged in Italy for example by Cerletti, Bianchi and, more recently, by D'Agata (1950), who gave an excellent historical survey of present knowledge about oligodendroglia.

Oligodendrocytes occur in the grey matter as 'satellite' cells where they are accompanied by a mass of nuclei of the neuroglial type (Orton, 1914). They are to be found lying between the basal processes of many of the large pyramidal cells in relation to that part of the cell process not covered with myelin but in close association with the point of origin of the axis cylinder. Their concentration in the cerebral cortex decreases from the deepest layers outwards. In the white matter they occur as 'interfascicular' cells and it is here that they are most numerous and have larger cell bodies and protoplasmic expansion than they have in the grey matter (Penfield, 1928). They occur in continuous rows between the medullated sheaths, sometimes in chains of 20 - 40 at a time (McAlpine, Compston & Lumsden, 1955). Penfield's description of the interfascicular oligodendrocytes said that the longer expansions passed upwards and downwards upon the medullated tubes of the nerve fibres and that the smaller expansions wrapped themselves around the tubes so that the myelin was 'enclosed' in a loosely woven net of expansions. It was notable also that these expansions/

expansions formed no specialised anchoring terminations comparable to the pial or perivascular 'foot' of the astrocyte. Lumsden and Pomerat (1951), by means of tissue culture studies, showed that in life the "processes" of the interfascicular cells were not the fibres they seemed to be in stained preparations but continuous membranes. They believed that these membranes formed a complete sheath "outside" the myelin sheaths, and they described the processes as fanning out into extremely delicate cytoplasmic veils. Glees (1955) going further than Robertson, Hortega and Penfield, claimed that, if successfully stained, oligodendrocytes were similar to astrocytes and pointed out that Penfield had noticed in young animals transitional forms between oligodendrocytes and astrocytes. David (1957) also pointed out that it was difficult to distinguish between astrocytes and oligodendrocytes by other than tissue culture methods and that the terms astrocyte and oligodendroglia referred not so much to morphological and cytochemical entities as to the effects of silver diamine solution on brain tissue, the differential identification of these cells relying on subtle differences in redox potentials and that when Nissl stains were used it was not possible to distinguish between the two. Ravens, Adamkiewicz and Groff (1955), in a histogram, also showed transitions of oligodendrocytes to protoplasmic and fibrillary astrocytes.

Functional studies of mature oligodendroglia have confirmed that its cells are actively motile. Motility in oligodendrocytes was first suggested experimentally by/

by Canti, Bland and Russell (1935) who demonstrated rhythmic pulsatility in oligodendrocytes in culture. Lewis (1950) produced motion pictures of neuroglia in tissue culture (from the brain of a 7-day chick cultivated in a fluid medium) which showed migratory activity of exceedingly long threadlike cells and, although the exact identity of the cells Lewis showed was uncertain, they were said to be very like oligodendrocytes. Kulenkampff (1952a) studied the behaviour of neuroglial cells, which were presumably 'satellite' cells, in the anterior horns of the spinal cord of the white mouse during muscular activity. He later (1952b) expanded his findings by a statistical study, based on a count of 53000 anterior horn cells, of variations in the nuclear size of the neuroglial cells following such activity and concluded that during such activity there was a migration of glial cells towards the anterior horn cells. The glial changes accompanying maximal exhaustion in the nerve cell were however reversible and there appeared to be a return to a normal distribution of glial cells after 4 hours of rest. Geiger (1956), in *in vitro* tissue cultures of adult brain cortex, observed, similarly, by means of time-lapse photography, relatively rapid amoeboid movements of the glial cells associated with neurones. The account by Kulenkampff seemed to imply that the return to a normal disposition of the glial cells, during the 4 hours after exhaustion of the nerve cell, was effected by a simple reversal of the process he had described, i.e. by a migration away from the nerve cells of those satellites which, during neuronal/

neuronal activity, had been drawn closer. An alternative explanation is that satellite cells drawn in during nervous activity subsequently migrate down the axon of the cell to which they had been attracted to become interfascicular glial cells. Such a hypothetical and speculative mechanism would offer an explanation for the constant metabolic turn-over of brain lipids in the adult brain which was demonstrated by Sperry & Waalsch (1950). Moreover, Lumsden and Pomerat (1951), improved, by time-lapse cine photomicrography, that oligodendrocytes extracted from the corpus callosum of adult rats, and presumably therefore of the interfascicular type, also exhibited a characteristic 'tug-of-war' rhythmic pulsatility.

It was Cajal who first suggested the myelinogenetic function of the interfascicular oligodendroglia similar to that of the Schwann cells. This suggestion was substantiated by Hortega (1919) who concluded that these cells carried to the nerve fibres the necessary trophic materials for the elaboration of myelin. He based his views on (1) the proximity of the cells to the myelin sheaths (2) their similarity to Schwann cells (3) their abundance in areas of active myelination (4) the presence of an increase of intracellular granules during the process of myelination. Penfield (1928) further confirmed Hortega's finding and views on this question and suggested that oligodendroglia played a role directly secondary to that of the neurone enabling it to maintain perfect functional activity over a great length - several feet in the case of Betz/

Betz cells. Berliner's (1931) cytological studies of the retina of the rabbit lent further strong support to Hortega's hypothesis for he showed that the rabbit retina was peculiar in that it was characterized by elongated areas of myelinated nerve fibres between which occurred numerous nuclei identical with the nuclei observed in the rows of glial elements in the optic nerve. He showed that the cells among these myelinated retinal fibres were definitely oligodendrocytes and that their processes appeared to be wrapped around the myelin sheaths. Now, the eye of the rabbit is distinguished from that of other mammals not only by the presence of myelinated fibres but also by the absence of the lamina cribrosa and it is probable, furthermore, that it is the absence of this structure which allows oligodendrocytes to migrate into the retina to produce there the peculiar myelination which characterizes it. Greenfield (1933) agreed with Hortega, Penfield and Berliner that the proper function of the interfascicular oligodendroglia was to control the nutrition, and the maintenance of the structural integrity, of the myelin sheath. McAlpine, Compston and Lumsden (1955) believed that the constant daily formation and maintenance of myelin may indeed be the sole and chief function of the interfascicular oligodendrocytes.

It is now considered probable that in the formation of the myelin sheaths in the nerve fibres of the central nervous system a mechanism similar to that in peripheral nerves occurs. The formation of the myelin sheath in peripheral nerves has been investigated from this cytostructural point of view by several authors. Thus Schmitt, /

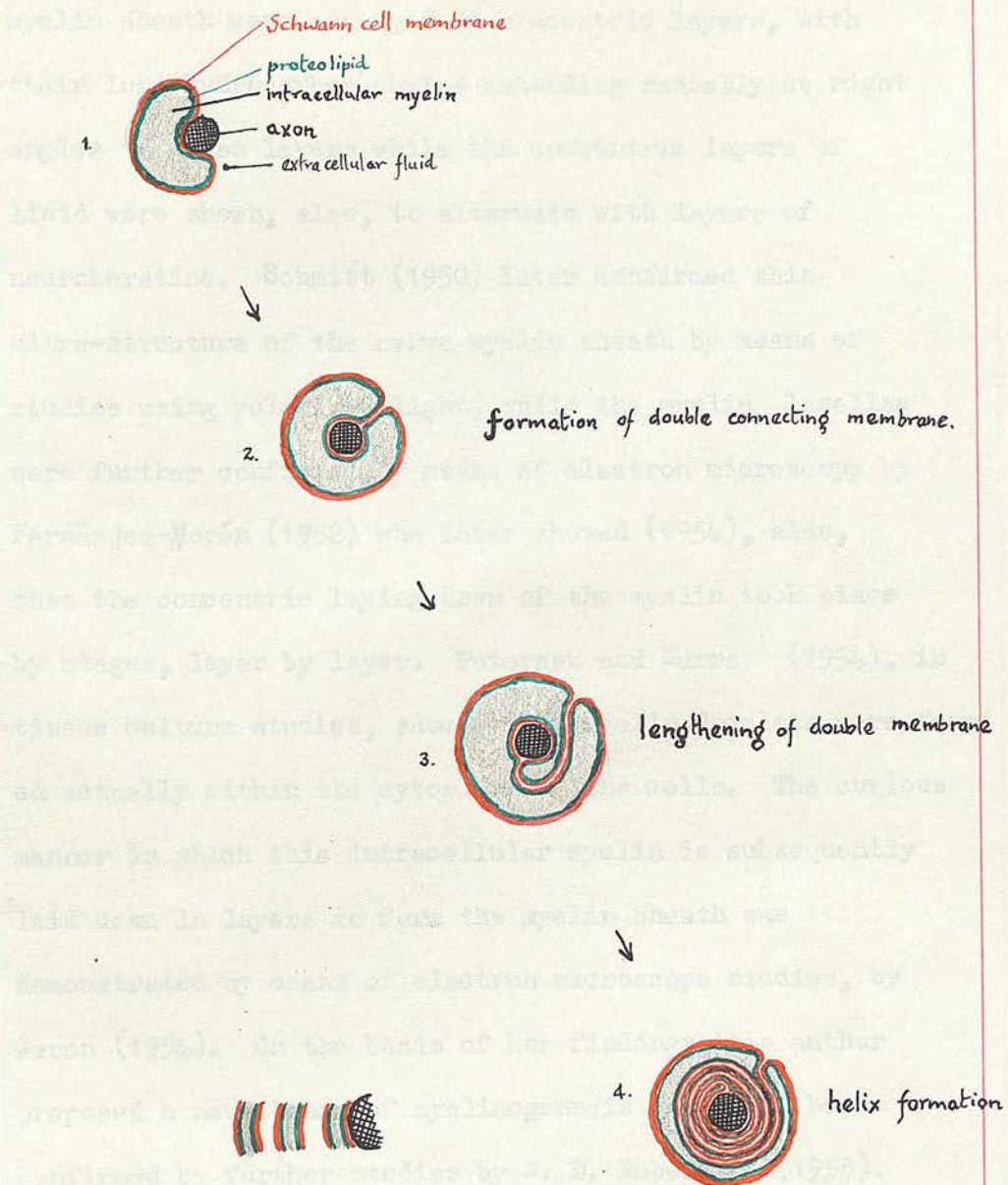


Fig. 3. Illustrating Geren's theory of myelinogenesis in the peripheral nerve fibre.

Schmitt, Bear & Palmer (1940) showed by means of x-ray diffraction studies, that the lipid molecules in the myelin sheath were arranged in concentric layers, with their long hydrocarbon chains extending radially at right angles to these layers while the concentric layers of lipid were shown, also, to alternate with layers of neurokeratine. Schmitt (1950) later confirmed this ultra-structure of the nerve myelin sheath by means of studies using polarized light, while the myelin lamellae were further confirmed by means of electron microscopy by Fernández-Morán (1952) who later showed (1954), also, that the concentric laying down of the myelin took place by stages, layer by layer. Peterson and Murray (1954), in tissue culture studies, showed that myelin droplets were formed actually within the cytoplasm of the cells. The curious manner in which this intracellular myelin is subsequently laid down in layers to form the myelin sheath was demonstrated by means of electron microscope studies, by Geren (1954). On the basis of her findings this author proposed a new theory of myelinogenesis which has been confirmed by further studies by J. D. Robertson (1955). According to this theory the layered myelin structure of the sheath is due to a double membrane which is closely wound about the axon as a helix, the double membrane being continuous with the outer lamella of the myelin sheath and internally with the double axon-schwann membrane. Geren and Schmitt (1955) carried out electron-microscope studies which threw still further light upon this question. J. D. Robertson (1957) pointed out that it was clear that if lipid/

lipid and protein were added to the Schwann cell surface membrane and the volume of the Schwann cell was held relatively constant the total area of the Schwann cell surface membrane could best increase by an elongation of the surface-connecting membrane. Such an elongation could occur by a rotation of one, or both, loci of connection of the surface-connecting membrane with the axon or the outer surface. Myelinogenesis would procede by the elaboration of this spiral and finally by the zippering together of the loops of the spiral to form the compact myelin sheath.

In the meantime, Speidel (1950) had shown that the sheath cells migrating out from the central nervous system flattened themselves along the young nerves and moved slowly peripheralwards. They exhibited a marked affinity for nerve substance, multiplied by mitosis, became spaced at appropriate intervals and, during the early stages of nerve growth, before the deposition of myelin, moved freely. After settling down as part of a myelin unit they moved about much less freely but even then they were still responsive to irregularities and would replace lost portions of myelin provided the nerve substance remained alive. The sheath was laid down in segments, one segment for each sheath cell, myelination starting centrally and proceeding peripherally. Speidel, who said that it was only after a certain degree of maturity had been attained that peripheral nerve fibres became ensheathed with myelin, added that it was not clear what started off the myelination of a particular fibre - it was certainly not a question merely of age, nor could the theory that it was the assumption of function which was responsible for initiating the process be/

be rigidly maintained for this theory has been disproved in some instances. Speidel said that his own evidence indicated that the essential factor for the laying down and maintenance of the myelin sheath was successful end-connections of its fibre.

It is possible that in the course of development, and in association with the nervous activity which follows upon the achievement of successful end-connections of individual nerve fibres in the central nervous system, there is migration along the interfascicular spaces of oligodendrocyte precursors which have been drawn in towards the neurone in a manner similar to that described by Kulenkampff. Hamilton, Boyd and Mossman (1945) said that myelination of nerve fibres started from a point close to the nerve cell body and spread distally from this point along the nerve fibre so that presumably, during development, oligodendrocyte precursors in the grey matter migrate into the interfascicular spaces of the white matter. Penfield who had pointed out that they were often found in pairs, giving the appearance of having undergone direct division during this process of migration, had also mentioned that migratory spongioblasts developed into mature oligodendrocytes in response to some type of activity within the neurone.

The ontogenesis of oligodendroglia has been the subject of investigations and study over a period of many years. Vignal (1889), who ascribed the deposition of myelin during development to "Hüllzellen", believed the latter to be embryonal cells having the same origin as neuroglia and migrating from grey matter into white matter. Ford Robertson (1900a) supposed the cells which were later/

later called oligodendrocytes to be of mesoglia origin. Hardesty (1905) described small cells of signet ring form which "appeared" for the first time at the onset of myelination, with their cytoplasm wrapped round the medullating nerve fibres and which were not detectable at a later period. Hortega (1919) maintained that oligodendrocytes developed from ectodermal spongioblasts and that intermediate stages in their development could be discerned. Penfield, mentioning that the 'indifferent' cells of Kolliker (spongioblasts) had been said by that author to increase by division until a relatively late stage in development, also said that even in young animals, there were to be seen many migratory spongioblasts in little differentiated form which seemed to migrate and to develop into oligodendrocytes. Penfield described the interfascicular oligodendroglial cells as appearing late in embryonic life (but before the microglia) and as increasing rapidly at about the time of birth at which time their cell cytoplasm was more voluminous and their granules larger than those of adult oligodendroglia. Morrison (1931), who studied early myelination in embryologic tissue from pigs, cats, rabbits and human beings, showed the first appearance of myelin staining substance in the form of small round black nuclei - i.e. cells which took the myelin stain. These cells first appeared, he said, just outside the ventricular ependyma, and in considerable numbers, at a stage when as yet no fibre tracts were medullated. Morrison gave a camera lucida drawing of one of these cells stained with supravital technic and examined through polarized light to show the presence of intracellular cholesterol ester. He further/

further showed that when myelinization was complete there were no longer any of these myelin staining cells present. Morrison maintained that other stains showed them to be oligodendrocytes, saying that similar cells had been identified as oligodendroglial in an oligodendroglioma. He regarded them in fact as being oligodendroblasts - the precursors of adult oligodendrocytes. Morrison said that the same cells he had described as appearing first just outside the ventricular ependyma later appeared in sites where nerve tracts were exhibiting the myelin sheath and he demonstrated numerous myelin staining cells along these tracts pointing out that no tracts were medullated without being accompanied by hosts of these cells. On the other hand, when myelinization was complete there did not appear, any longer, to be any of these myelin staining cells present. It seemed as if they appeared before tracts were medullated, accompanied myelination and then disappeared when myelination was complete. Jones (1932) compared the ontogenetic to the phylogenetic development of oligodendrocytes and confirmed that the sequence of their development in the cerebrum was comparable to that in the spinal cord. Alpers and Haymaker (1934) while agreeing that the developing oligodendrocytes played an important role in myelinogenesis, added their belief that astrocytes also, at least in the 'premature' brain (i.e. in the brain of the premature infant) took part in this process. Kershman (1938) found that extra-ependymal mitoses of spongioblast precursors of oligodendroblasts were, in the cerebral hemispheres, most frequent in the subependymal zone. Some occurred in the lower/

lower intermediary zone or in the cortical plate and in the latter areas it seemed clear that the cells all arrived by migration from peri-ependymal regions and that no new elements were formed in situ. Godina (1951), who described the development and differentiation of all the macroglial cells, stressed the importance of their development from amoeboid spongioblasts of neuroectodermal origin settling during development at various levels of the cerebral hemispheres and he described how, before the filamentous processes of ependymal cells regressed, glial cells, different in appearance from the more mature cells, appeared at different levels of the hemispheres, in the germinal layer and in the intermediate layer.

It is probable that migration to the different layers is confined to the more primitive cells at an early stage and that only at a later stage do these cells multiply and mature in situ and migrate from the grey to the adjacent expanding white matter but the important terminal or maturational stages in oligodendroglial development are, in fact, almost unknown. Penfield said that oligodendrocytes were present throughout the nervous system at birth, particularly in the white matter, and that they remained practically constant in number throughout life. Greenfield (1933), however, said that although in the unmyelinated fibre systems of the human brain at birth there were numerous oligodendroblasts, very few mature oligodendrocytes were present. Also, Kuhlenbeck's (1950) emphasis, on the fact that the molecular zone of the newborn infant, unlike that of the adult, was very cellular, suggested that the reduction/

reduction in cellularity which takes place during postnatal life might be related to the migration of oligodendroblasts into the white matter during the postnatal expansion of the brain. This author also mentioned that embryonic cells may persist in this zone to form the basis of neuroectodermal tumours and work on the localization of oligodendrogliomas has indicated that they tend to arise in those neocerebral regions of late development-regions in which oligodendroblastic migration and maturation is presumably most tardy. It is also of interest that Ravens, Adamkiewicz and Groff (1955) found that of 36 oligodendrogliomas, 24 were in the left hemisphere and 12 in the right - a ratio which suggests significant differences in the rate of oligodendroglial differentiation as between the two hemispheres but unfortunately these authors gave no indication of the handedness of their patients. Linnell and Tom (1931), describing postnatal morphological changes in the oligodendroglia of the white rat, confirmed that there was a continued and progressive differentiation of these cells in connection with postnatal myelinogenesis while in the human brain also the continued postnatal maturation of oligodendroglia is implied by that differentiation of neuronal processes which continues to take place even into adult life and which is accompanied or followed by the continued myelination of these growing nerve fibres. If, in the human brain, with its prolonged period of morphogenesis, oligodendroglial maturation is indeed correspondingly prolonged, its specific developmental vulnerability during postnatal life would presumably be in/

in particular relation to the terminal phases of its myelinogenetic function.

Biochemical aspects of myelinogenesis.

Quantitative biochemical studies of the myelinogenetic process have shown that most of the postnatal growth of the human brain is attributable to the deposition of myelin in the central white matter (Gray's Anatomy, 1950). Sperry (1955) said that during the first 7 months of foetal life there was little quantitative change in the total lipids and that from then onwards the rapid increase in lipids was more marked in the white matter than in the grey matter. While the adult level of lipid content was 'almost reached' in the grey matter by the 3rd month of postnatal life, the increase in the total lipids of the brain continued from that age until the 10th year of life, so that the process of lipid formation during this particular period could be regarded as taking place chiefly in the white matter. The chemistry of the early formation of the myelin of the white matter has been investigated by many authors and, indeed, according to Sperry (1955), the most numerous and extensive investigations of the biochemistry of the brain during early development have been concerned with those lipids which are involved most intimately in myelin metabolism. In the brain of the rat early lipid formation is greater in non-specific forms than in the form of 'myelin' and the former is not equalled and surpassed by the latter until the 20th day of postnatal life (Waelsh, Sperry and Stoyanoff, 1941). Sperry (1955) pointed out that, although the greatest rate of lipid formation/

formation in rat brain took place just after birth this stage definitely preceded the stage of actual myelin deposition. These findings suggest that large amounts of the lipid formation in the brain are not immediately or mainly in the form myelin and perhaps that lipid is first formed in the brain in sites other than the myelin sheath and it is subsequently transported to the sheath by oligodendroglial cells migrating from the grey matter into the white. Sperry also called attention to the possible importance of the variations which seemed to be characteristic features of some of the data relating to lipid deposition in the brain during the period of childhood.

Qualitative biochemical studies indicate, with regard to the lipid content of the myelin sheath of mammalian nerve fibres generally, that the three principle components are (1) cholesterol, (2) cerebroside and (3) phosphosphingoside and Rossiter (1955) pointed out that it is these same three lipids which distinguish the white matter of the adult brain from that of the relatively unmyelinated brain of the new born infant. Feigin, Wolf and Carter (1957) mentioned, in addition, (4) phosphatidyl serine and (5) plasmalogen. They suggested the possibility that, although these substances were already present in infancy in intermediate stages of myelin anabolism, they had not, at that stage, achieved that physicochemical structure which permitted the usual myelin staining. Tingey (1956) carried out comparative studies of the various lipid constituents in human brains at different ages. He found that the neonatal brain contained considerable/

considerable proportions of cholesterol and cerebrosides but negligible sphingomyelin. In the cortex, cholesterol and cerebroside reached adult proportions at 2 months while sphingomyelin was still only $\frac{1}{3}$ of the adult level even at nine months. In the white matter, on the other hand, there was an increase in sphingomyelin up to the age of 2 months and, from 2 to 9 months, in the cholesterol and cerebroside also - the latter reaching a maximum before the age of 5 years. He also found that the adult/infant lipid ratio was lowest for lecithin and highest for sphingomyelin and he considered that this suggested that the Weigert-Pal method of staining myelinated fibres was more closely correlated with sphingomyelin than with other lipids. Tingey's studies of lipid constituents were only comparative in nature and the later, absolute, increases in myelin lipids, dependent upon the growth of the brain which takes place between the age of 5 and 10, were not discussed. Sperry and Waelsch (1950) formulated a purely biochemical mechanism whereby the process of myelinogenesis could be brought to a standstill or at least to the low rate of lipid replacement which characterises the adult brain. They suggested that as the general oxidative metabolism of the individual increased during the period of myelination it sucked off an increasing proportion of the pyruvic acid and acetic acid into the tricarboxylic acid, thus reducing the available acetic acid and eventually bringing myelination more or less to a standstill. However, that the brain lipids in the adult continue, nevertheless, to be in a state of constant metabolic turnover, or 'dynamic equilibrium', was confirmed by Sperry and Waelsch (1950)

by/

by means of studies with the stable isotope deuterium.

The later phases of the maturation of the myelin sheath, especially those taking place mainly beyond the age of 10, although quantitatively insignificant, may be specially important qualitatively and structurally and it is indeed to the imprecise nature, chemically, of that which is stained by 'myelin' impregnation techniques (David, 1957), and to particular ignorance about the biochemistry of these later stages of 'myelin' metabolism that the imprecision of our knowledge about the chronology of the terminal phases of myelinogenesis in the cerebral hemispheres is largely due. The very constituents of the myelin sheath of special importance in the maturational period of its development are incompletely known, but, in addition to the constituents already enumerated, porphyrins, the various enzymes and, in particular, the neurakeratin proteolipids call for special mention.

Goldberg (1957) pointed out that some tetra-pyrrole, of which porphobilinogen was a precursor, may be essential to full myelination and also that the porphyrin-like structure of Vit B12 demonstrated that at least one other tetrapyrrolic substance was essential. It was Klüver (1944) who showed that porphyrins normally appeared, but at a comparatively late stage, during the maturation of the white matter, their development being contingent, perhaps, upon light penetrating the tissues of the body once intrauterine life is over. Klüver studied with a mercury vapour lamp and a Corning filter No.5874 the fluorescence spectrum of the normal central nervous system before exposure to daylight and drew particular/

particular attention to the 625 band which, although it rapidly disappeared under the influence of light, could regularly be observed when the (mature) white matter of warm blooded animals was examined by the method he described. The position in the spectrum of the 625 band, Klüver argued, strongly suggested the presence of porphyrin and he claimed, moreover, that by chemical analysis he had never failed to extract, from regions of the white matter emitting this band, a porphyrin having, in point of fact, the characteristics of a coproporphyrin. He said that in warm blooded animals, in which alone the 625 band appeared, this distinctive spectroscopic feature, was not present at birth, and only began to appear (but at an early stage) postnatally. Moreover it appeared only in the spinal cord at first but, later, in other regions also and eventually in the white matter of the cerebral hemispheres. The postnatal maturation of the white matter, at any rate in mammals and birds, seemed to him to be associated with an 'ascending porphyrinization' which followed the same topographical sequence as the earlier stainable myelination which had started much earlier in foetal life. Klüver, who pointed out, further, that the regions of the brain from which the emission bands of porphyrin were absent were in fact the regions in which the absorption band of cytochrome were clearly present, argued from this observation that coproporphyrins were derived from cytochrome and suggested that porphyrins were necessary during particular phases (presumably late phases) of development of the white matter. Finally, after drawing attention to the fact that the 625 band was absent from non-glial portions of cranial nerves//

nerves Klüver raised the question of the occurrence of porphyrin in white matter being correlated with the presence of (mature) oligodendroglia. It seems probable that the production of porphyrin is indeed particularly associated with a late and strictly postnatal stage in the maturation of the myelin sheath and of its oligodendroglia.

The enzymatic changes in the maturing white matter have received some attention but, as David (1957) pointed out, very little is known, as yet, about the histological distribution of enzymes in the brain. Sperry (1955) said that Youngström had verified, in man, that an increase in the concentration of cholinesterase coincided with the development of functional activity in the white matter and the topographical sequence of the appearance of this enzyme was said to be; midbrain and medulla, spinal cord, diencephalon, basal ganglia and, finally, cerebral hemispheres, a topographical sequence which broadly corresponds both to that of stainable myelin and of porphyrinization. That the pseudocholinesterase enzyme may be concerned with the metabolism of myelin and neuroglia (rather than, as had been supposed, with the conduction of nervous impulses) was suggested by Ord & Thompson (1952). Cavanagh, Thompson & Webster (1954), who pointed out that white matter was particularly rich in pseudocholinesterase, concluded from its activity in gliomas that this enzyme was present actually within the glial cells. Naidoo & Pratt (1954) showed, in ^{the} postnatal maturing cerebral cortex of the rat (as distinct from the central white matter), that there was an increase in activity of the enzyme adenosine 5⁺ phosphatase which reached a maximum between the fifteenth and/

and the eightieth day of life and, because the increased activity of this enzyme postnatally was observed in relation to intracortical nerve fibres, the authors thought that it might be related to the myelination of these fibres.

Little is known of the ontogenesis of the neurokeratin proteolipids in the white matter of the human brain although Svet-Moldavskaya and Svet-Moldavsky (1958) have studied the ontogenetic development of these components in rabbit brain. 'Neurokeratin', a structural rather than a secretory protein, was first isolated by Ewald and Kuhne (1877) but the nature of neurakeratin proteins was unknown until the work of Folch & Lees (1951) and Le Baron and Folch (1956). Of these neurokeratin proteins, the so-called proteolipids A & B constitute about 5% of the total solids of the white matter and may prove to be of special relevance for diffuse sclerosis because they are endowed, according to these authors, with encephalitogenic properties (see page 219).

Topographical aspects of myelinogenesis.

Grossly stainable myelin becomes apparent for the first time extracerebrally, and during the prenatal period, in those fibre systems which function earliest and are oldest phylogenetically. It was reported, by Hamilton, Boyd & Mossman (1945), as starting, in the fourth month of foetal life, in the cervical region of the spinal cord. The intersegmental fibres in contact with the anterior grey columns were said to be the first to become myelinated followed, a little later, by the ventral commissural fibres and by the ventral root fibres - which are/

are myelinated at the sixth month of foetal life. From the cervical region the process extends in a caudal and rostral direction. The medial longitudinal bundle is the first of the brain tracts to show myelination (sixth month), but it is soon followed by the vestibulo-spinal, reticulo-spinal and tecto-spinal tracts. The spino-cerebellar and the spino-thalamic tracts myelinate at the seventh month but afferent thalamic pathways are not myelinated as far as the thalamus until the eighth month. Myelination only begins to reach the spinal portions of the descending motor tracts (pyramidal and rubrospinal) at full term. The cranial nerves of the medulla and mesencephalon show the first signs of myelination at about the sixth month of foetal life - the motor fibres being myelinated before the sensory. The vestibular nerve is the first sensory root to be myelinated; the cochlear is distinctly later. The globus pallidus and the thalamus, which belong to the paleo-encephalon also myelinate before birth but the caudate nucleus and the putamen, which belong to the neoencephalon, do not myelinate until after the 5th month of postnatal life (Adie and Critchley, 1927). The myelination of the optic nerve begins about full term but the macula, unlike the rest of the retina, is not fully developed until the child is a few months old. Now the maculopapillary bundle of nerve fibres, after sweeping over the temporal part of the optic disc, continues posteriorly and eventually becomes centrally placed within the nerve. In view of the comparatively late maturation of the macula, it may be, therefore that this core of fibres completes its myelination at a relatively/

relatively late stage compared with the surrounding optic nerve fibres.

It is, however, the myelination of the central white matter of the cerebral hemispheres which is of the greatest relevance for the present enquiry. Dodgson (1954) said that a dense plexus of neurofibrils first became demonstrable in the region of the central fissure in the 7 months foetus. At about the same time myelination spreads upwards to the cerebral hemispheres and quickly becomes established in the primary sensory and motor zones. Vogt (1928), in a paper on the cyto- and myelo-architectonics of this paracentral region of the cortex included a diagram showing the first of the fibres to myelinate and they are seen to consist of projection fibres from both the pre- and post central regions and of subarcuate fibres connecting the two regions. According to Gray's Anatomy (1950) the myelination in the cerebral hemispheres appears first not only in the afferent fibres to the somesthetic area in the post central gyrus but in those to the hippocampal formation and, shortly afterwards, in the afferent fibres leading to the visuo-sensory and audito-sensory cortical areas. In general, myelination is established first in afferent fibres to the cortex and then in the fibres of the deeper cortical layers. From this site it spreads both superficially and deeply, the deep spread into efferent fibres being, successively, along the subarcuate fibres, the short association fibres and, eventually, along the longer association, commissural and projection fibres which pass into the depths of the white matter. The 'horizontal' spread of myelination from the primary centres over the rest of the cortex/



cortex was first studied by Flechsig (1898) who investigated in detail the chronological sequence of myelination in the fibres of the white matter immediately subjacent to the cortex. Flechsig's work, which has been substantially confirmed by Jakob and others, showed that projection fibres (mainly from 'primordial' zones) tended to myelinate before correlation fibres (mainly from zones of late development). He described, originally, 40 cortical fields, dividing them into 'primordial', 'intermediate', and 'terminal' zones, but later he made certain changes in his groupings. Flechsig (1901) protested when Hitzig drew a map from his new data without his authorization, but Bailey and von Bonin (1951) were not deterred from drawing a similar map from Flechsig's (1920) final data when he had increased the number of zones to 45. Their map distinguished:-

- (a) zones myelinated at birth (F1 - 17)
- (b) zones myelinated during the first month (F18 - 36)
- (c) zones myelinated later (F37 - 45)

The myelination of Flechsig's primordial zones is rapid and they are fully myelinated locally at birth although the myelination distally of their longer efferent fibres is by no means complete for the 'pyramidal' fibres have at that stage only myelinated as far as the decussation of the pyramids. Myelination spreads rapidly from the primordial zones into the intermediate zones in early infancy and this early spread is followed by the longer drawn-out spread from the intermediate zones into the still growing terminal zones. Flechsig (1901) pointed out that not only was the comparative size of these 'terminal zones' much greater in man than in the lower animals but that the completion/

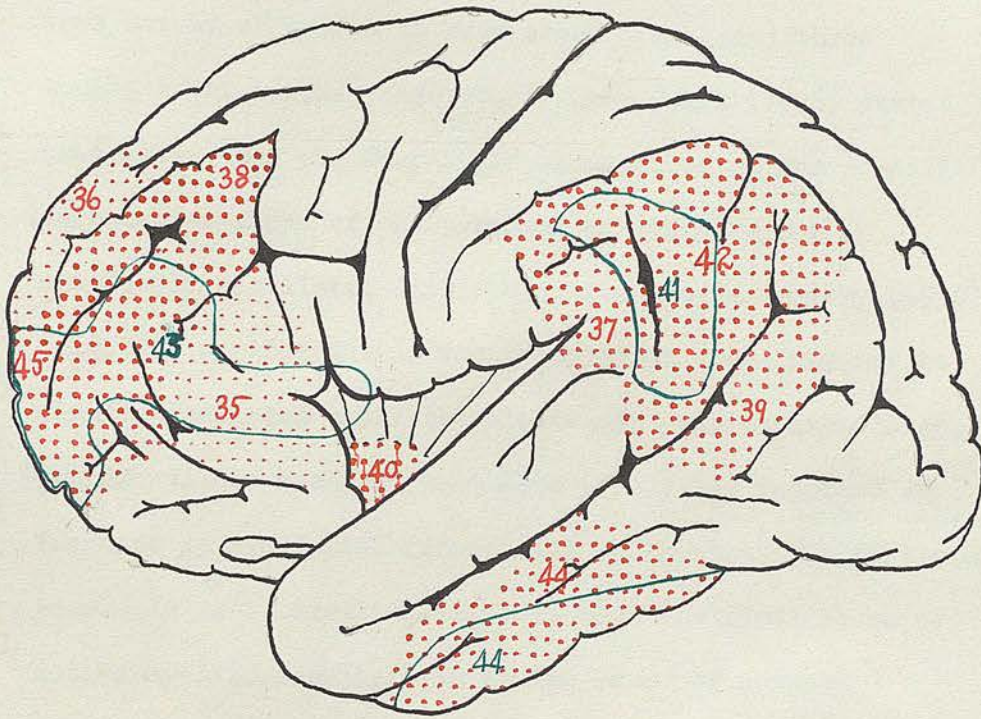


Fig. 4. Diagram (after Bailey and Von Bonin) indicating the last two of the intermediate (35 and 36), and all the terminal, myelinogenetic zones of Flechsig (37 - 45). Zones on the medial surface are indicated in green.

completion of their development was more protracted. He said that the formation of myelin in relation to these terminal zones did not start until after the completion of the first month of the child's life but he did not specify how protracted the subsequent process was and, indeed, said no more than that numerous fibres were devoid of myelin in some areas even (sic) three months after birth. However, Le Gros Clark (1946) stated explicitly that the fibres and connections of the so-called association areas of the cerebral cortex were not completely medullated until puberty. Gray's Anatomy (1950) said that myelination in the association areas may not be finally completed until the eighteenth year or even later, and it will be recalled that Kaes (1907) had reported an increase in myelinated fibres even up to about the fortieth year. It seems certain, in fact, that the final phase of active myelinogenesis, even in the sense of grossly stainable myelin, is, in relation to these areas of late development, spread out not over a comparatively short period in infancy but over the whole of childhood and adolescence.

While it may be, in view of Kaes' observations, that cerebral dominance is to be correlated with the earlier myelination of the dominant hemisphere as compared with that of the non-dominant, the question of myelinogenetic differences between the two hemispheres has not been adequately studied as yet. Detailed studies have, however, been made of the developmental myelinogenetic activity of the inferior frontal gyrus, which corresponds to Flechsig's myelinogenetic zone No.35 (F35). Aranovitch (1939),

(1939), describing the maturation of myelin in all the various cortical areas concerned with the development of speech function, found that myelin was present in the greater part of this area at birth, that further development of myelin took place in part of it during the 1st month of life, that between the 6th and 8th month myelination reached the tangential fibres and that these underwent further differentiation between the 2nd and 3rd year. Similar chronologically detailed studies of the terminal myelination of the parietal, temporal and prefrontal 'association areas' have not, so far, been carried out and the maturation times of the remaining individual terminal zones of Flechsig (F36 - F45) remain obscure. Assuming that the order of grossly detectable myelinogenesis described by Flechsig is maintained during its more subtle, terminal, stages the studies of local cortical cyto:architectonic maturation described above suggest that a provisional estimate of myelinogenetic times for these terminal zones may be drawn up. This is shown in Fig. (5)

To an increasing extent, in the later zones, the final stages of the myelination of the myelinogenetic 'units' will be located at the distal ends of their efferent fibres, rather than locally, i.e. it will be in what are, in fact, the afferent fibres of other zones.

Functional aspects.

The precise relationship between the structural and the functional maturation of the central nervous system is uncertain. Hamburger and Levi-Montalcini (1950) pointed out that ~~the~~ nerve cells became functional neurones long before/

before terminal neurone size was attained i.e. long before they were morphogenetically mature and Coghill⁽¹⁹²⁹⁾ and others proved that nerve fibres conducted impulses before they were myelinated. Nerve fibres were said by Gray's Anatomy (1950) to be incapable of conducting impulses until they had acquired their myelin sheaths but Cunningham's Anatomy (1931) stated that the short association fibres of the brain assumed their sheaths of myelin and became functional only after birth when intellectual effort and education had stimulated different portions of the cortex to act in harmony and in conjunction with each other - and thus implied that myelination followed, and was perhaps a result of, functional activity. More recently, Gerard (1950) quoted evidence that functional activity acted, indeed, as a stimulus to the glia and, through the glia, to myelination also. Other investigators have contended that nervous function at a mature level and beyond the level of simple reflexes, is only rendered possible by the complete myelination of nerve fibres and, in particular, Langworthy (1933) stressed that nervous function of a high order involved important questions of the accurate timing of the arrival of impulses and he pointed out that myelination had important bearings on that requirement.

The spread of the functional maturation of the cerebral cortex, as indicated by the spread of its electrical maturation, corresponds to the sequence of cytoarchitectonic maturation already outlined. Thus, Smith (1938) in electroencephalographic investigations on infants from the time of birth onwards, observed that the waves which began to/

to be recorded at the age of one month appeared at first only in the region of the precentral gyrus, while E.E.G. studies by Lindsley (1939), Henry (1944) and Hill (1955), gave analogous results for later childhood. Grossman (1955), who gave full bibliographical references to recent systematic studies of the ontogenesis of E.E.G. patterns in man, confirmed the fact that the evolution of mature neocortical function started in the primordial sensori-motor zones and advanced horizontally from area to neighbouring area, and showed that the process took place also in depth, i.e. from the deeper layers upward. It was uncertain, according to Hill (1955), at what age the overall adult pattern of E.E.G. was reached but electrical maturity was generally regarded as taking place at some time between 18 and 20 years, although in many individuals it was reached earlier while in some others it was said not to occur until the 3rd decade of life. The spread of functional maturation of the cortex, as indicated by behavioural development, has been correlated experimentally with the spread of myelination in kittens, by Tilney and Casamajor (-) and Langworthy (1929) has investigated the same question in kittens, opossums and human beings. However, very little is known about the neuroanatomical basis for the maturation in the human infant of those postnatal behavioural patterns which are not specifically human - such as reflex grasping in the first few months of life, reflex groping in the late second or third month, anticipatory motor preparations for being picked up at the fourth month and holding up of the head at the fifth month. Furthermore, the emergence of specifically human behavioural patterns can be correlated with the spread of cortical maturation only in/

in the most tentative way. The embryology of these behavioural patterns in postnatal life has been well studied and described by Gesell and Amatruda (1948), McGraw (1943), Piaget (1928) and others and further studies of this kind, in association with growing knowledge about the localization of function in the cortex should complement the comparatively recent histological and electrical studies of the late structural-functional maturation of the cortex including that of the characteristically human, 'association' areas of the parietal, temporal and frontal lobes.

Already it may be said that the earliest of the specifically human modes of behaviour to appear, viz. speech, is dependent upon the structural maturation of the inferior frontal gyrus (which corresponds to Flechsig's area 35) and it is established that structural maturation is completed in this area by the age of 3 years. The next characteristically human attribute to appear would seem to be the achievement of the erect posture. Now, this achievement is dependent upon the development of adequate tone in the appropriate muscles of the lower limbs and it is tempting to correlate it with maturation of the corticospinal fibres arising most anterior to the motor area for the lower limb, i.e. from Flechsig's next myelinogenetic zone, his area 36, although the cortical basis for this behavioural advance is, in fact, still unknown. On the other hand, the freeing of the hands from a purely prehensile and locomotive function involving the acquired ability which gradually develops to beyond the end of the first year to relax the grasp, and which is made possible by achievement of the erect posture was carefully studied by

Adie/

Adie and Critchley (1927). These authors, who investigated the phenomena of forced grasping and forced groping in three cases of brain tumour, concluded that the syndrome was an expression of disease in the frontal lobe and argued that the pathways which were disturbed when infantile forced grasping and groping re-emerged in adult patients were cortico-spinal pathways from the upper and posterior part of the frontal lobe but not the primary motor tracts from the precentral gyrus. Their findings, therefore, suggested that the developmental suppression of the grasp reflex depended upon maturation of this cortical region. Now, Flechsig's area 37 corresponds to the supramarginal gyrus which is generally acknowledged to form the cortical basis for manual stereognostic sense but his next zone, area 38, which is situated, in fact, anterior to the premotor area for the hand, may well be the region, the maturation of which underlies the normal developmental disappearance of reflex grasping and groping. No special functional significance can be definitely attributed to the maturation of Flechsig's next zone, area 39, but, situated as it is in the occipito-parietal region, its maturation may perhaps underly the increasing hand-eye co-ordination of the preschool child and the correlation of visual, with tactile, space. The faculty of reading, which develops during early school days, has already been attributed by some to the functional integrity of the medial surface of the parietal lobe (Flechsig's area 41) although most authors associate it with integrity of the angular gyrus (Flechsig's area 42). The functional significance of the structural maturation of the remaining association areas/

Flechsig's Myelino: genetic Zones. No.		Sites	Times of Maturation.
Intermed: iate	35	Broca's Area	Late Infancy
	36	Superior Frontal	
Terminal	37	Supramarginal gyrus	Kindergarten
	38	Middle Frontal	
	39	Parieto-occipital	
	40	Lower part of Insula.	Primary School
	41	Medial Surface of parietal lobe	
	42	Angular Gyrus	
	43	Medial Surface of Frontal Lobe	Secondary School
	44	Inferior Temporal	
	45	Pre-frontal	Adolescence.

Fig.5. Table indicating tentative and provisional times for the full maturation of Flechsig's last two intermed: iate, and his nine terminal, myelinogenetic zones.

areas (Flechsig areas 43, 44 and 45 in the temporal and parietal regions) is still uncertain but at least it may provisionally be presumed that these zones are concerned with the higher mental functions and that they complete their maturation only during later school days and in adolescence. These necessarily tentative and provisional topographical and chronological correlations are illustrated in Fig. 5.

Summary.

The postnatal growth of the brain is known to continue right up to adult life but different cortical areas expand at different rates and at different stages. The altering pattern of gyri and sulci which is observed during this period is such as to indicate that late cortical growth takes place mainly in the so-called association areas of the parietal, temporal and frontal lobes but it has only been recently that the cytoarchitectonic aspects of this late growth have been investigated systematically. Even now, scarcely any attention has been given to the corresponding late growth of the underlying white matter and myelinogenesis is still widely assumed to be completed during early infancy. Nevertheless this process is now known to continue, if in a progressively more subtle mode, up to adult life, the structural changes taking place mainly in relation to the gliovascular element and, more particularly, in relation to the interfascicular oligodendroglia, which is responsible for the formation and maintenance of the myelin sheaths, while the biochemical aspects of myelin maturation are probably in relation mainly to the metabolism, within the oligodendrocytes, //

oligodendrocytes of the neurokeratin proteolipids. It may reasonably be assumed that this terminal phase of myelin maturation, although longer drawn out in time than has previously been realized, follows the same topographical sequence as that more gross myelinogenesis which was long ago described in such careful detail by Flechsig. It may also be assumed that it is closely related both to the spreading functional maturation of the cortex in postnatal life and to the psychological and behavioural development of the individual which this subserves.

3. THREE CASES OF SUBACUTE DIFFUSE SCLEROSIS.

CASE 1. AN INFANT.

MARY S. (died aged 2 years 4 months).

Presenting features - Failure to walk. Speech deterioration

ANAMNESIS.

Most of the details of the following history were obtained from the mother but the father also contributed information. Both parents were intelligent and co-operative.

Family History.

Father - aged about 31, was a photographer of asthenic build who had suffered from pulmonary tuberculosis nine years previously. The paternal grandparents were said to have been healthy.

Mother - aged 29, was in good health. At the age of 10 she had herself attended hospital on account of a disability in walking. Unfortunately, on enquiry, the case records were found to be incomplete and inconclusive but she had received treatment appropriate for osteochondritis of the hip and it was said that an irregularity of the inner quadrant of the head of the left femur had been detectable by X-ray. She had made a complete recovery from this. During the latter part of her pregnancy she had had some 'kidney trouble' and also, a month before the patient was born, a fall. The maternal grandparents were said to have been healthy.

Siblings - (1) Brother (aged 6) alive and healthy
(2) Brother (aged 5) alive and healthy (3) Patient (aged 2.2/12).

The mother's sister was said to be a nervous person
and/

and a cousin to have had poliomyelitis but apart from this there was no record of mental or nervous illness among other relatives.

Personal History.

The patient was born at home on 14th May, 1954 after a labour which was normal and in which instruments were not used. The birth weight was 9 lbs. There was no neonatal jaundice and she was bottle-fed. She had a normal early infancy and in general was happy and contented. She was not prone to illness, there were no convulsions and teething was normal except that when cutting her first four teeth she would put her hand to her ear and would seem to be having some earache.

She developed reflex grasping and groping and showed movements anticipatory to being picked up at the normal times. She first lifted her head at 5 months, sat up shortly afterwards and her first attempts at walking were at 6½ months. Although the first evidence of her illness, in the field of learning to walk, could be dated to the age of nine months, she nevertheless made further progress in walking up to the age of 15 months when she could walk holding on to one finger.

Her speech development also began normally. At 9 months she was saying Mamma and Dadda, at 1 year she was putting words together, shortly afterwards she was beginning to say simple nursery rhymes and her speech continued to progress normally until about the age of 18 months.

The parents noticed that she was becoming predominantly right handed. However, she tended to keep her mouth open and to drool saliva, never learned to feed herself satisfactorily, /

satisfactorily, and did not gain bladder or bowel control.

Previous Health.

She had had no particular illnesses in early infancy. After the onset of her main illness she had measles, at the age of 14 months, and was quite ill with it for two days but experienced no complications. She was given B.C.G. inoculation shortly before the age of 2.

Present Illness.

The patient had appeared to be a perfectly normal infant until the age of nine months. It was then noticed that her efforts to walk were hindered by the fact that she tended to turn her feet outwards. The mother did not take this very seriously because she believed that she herself had been affected in the same way as an infant and, moreover, the patient had been seen by the family doctor who had adopted a reassuring attitude. However, slowness in making progress with learning to walk persisted and, at 12 months, as she was still not progressing as expected, medical advice was again sought, as a result of which at 15 months, she was referred to an Orthopaedic Clinic.

There, she was found to have a marked flaccid talipes valgus of both feet, more marked on the left, and it was decided to try to rectify this by putting the legs in plaster. This was done for two successive periods of two months but, at 19 months, when the plasters were removed, there was no improvement in her legs. She still sat up normally, and she was given further exercises at the clinic. In spite of the exercises progress in learning to walk seemed to have halted and soon, indeed, walking ability began/

began to regress.

From that time the mother began to wonder if her child was mentally defective, particularly as she had overheard some of the nurses refer to the child as a 'spastic', or a 'backward' child. However, speech development had, in the meantime, continued normally. At the age of 18 months it, too, became stationary and for three or four months no further progress seemed to be made. She also began to have outbursts of crying and in particular always cried when the bowels moved. At the age of about 20 months, her trunk also began to flop to the side so that she became unable to sit up properly. Her head, also, started to droop and fall forwards. Although at 21 months it had been noted that there was no spasticity in the legs, at 23 months moderate spasticity in both legs was found and it was also noticed that the hands were developing a claw position. At the same time, her speech development, which had been stationary for a time, began actually to deteriorate and within a further month or two, except for occasionally asking for her pot, she was saying little more than 'Mamma' and 'Dadda'.

As the family had then moved to Ayr, she was examined by the new family doctor, Dr. Walker, who referred her to the pediatric clinic at Seafield Hospital, Ayr and she was seen there, at the age of 2 years, by Dr. Abramson, on 15th May 1956. It was noted that the child was unable to walk and that her speech was so poor that it could not be understood. Her sitting posture was hypotonic and her facial expression, perhaps because of muscle weakness, was rather empty, her mouth/

mouth hanging open and drooling saliva. Although the head kept dropping forward, the child was still able to support its weight by the anterior and posterior neck muscles if she was held horizontally on a couch. The eyes showed a spontaneous lateral nystagmus greater to the right than to the left. The arms were flaccid in tone and no reflexes were obtained. Voluntary movements were poorly controlled and co-ordinated. There was persistent flexion of the fingers suggestive of upper motor neurone damage and despite the general flaccidity it was thought that there was a suggestion of spasticity on passive manipulation of the fingers. They were flexed at the interphalangeal joints and the thumbs were not held across the palms. The lower limbs were definitely spastic by this time with a tendency to adduction of the thighs and hyperextension at the ankles. Muscle tone was high and tendon reflexes exaggerated. The cardiovascular, respiratory and alimentary systems seemed to be normal.

Dr. Abramson thought that there was a widespread lesion affecting upper motor neurones and co-ordination. He thought that a degenerative condition, such as Schilder's disease, was the probable diagnosis and that the mental deterioration was possibly more apparent than real. Certain special investigations were arranged on the same day and these furnished the following results:-

Lumbar puncture:- "Fluid normal in pressure, appearance and in constitution except for a rise in protein which was 110 mgm.%; sugar normal (66 mgm.%) and chloride 708 mgm.% Cells 1 per c.mm. This fluid suggests some non-infective process". Blood Count:- "shows a total white count of 12,500/

12,5000 with a normal differential count for her age and haemoglobin of 12.4 mgm.% which is near enough to normal". W.R. and Meinicke were negative in both the patient and her mother. Toxoplasma Tests:- "The patient was completely negative. The mother had a negative complement fixation test but had a positive dye test though it is of no significance regarding the baby's condition. Toxoplasmosis can be excluded". X-ray Report Skull and Spine:- "No apparent abnormality in shape contour or structure of skull bones. The cervical vertebrae appear fairly normal though there is some postural deviation of the upper thoracic spine. The same applies to the lumbar region though there is no evidence of abnormality in either area. The last lumbar vertebral and sacral spines are bifid".

Because of the possibility of Schilder's disease the child was, at 25 months, admitted to Seafeld Hospital for further observation and investigation. It was then reported that she had continued to show a progressive deterioration in walking and in muscle power. Although all the limbs had apparently been, originally, hypotonic, the legs had become more spastic and tended to cross over. It had also become more difficult to feed the child, who became emotionally distressed very easily. On admission she was found to be an unhappy child who was able to move very little in her cot and lay in the opisthotonic position. She had no cough, no cyanosis and no lymphadenopathy. Examination of the nervous system confirmed that her pupils were equal and reacted to light. Nystagmus was present. She was unable to support the head for more than a few seconds./

seconds. Although the legs were spastic and crossed the arms were still flaccid. The reflexes were brisk. After four days in hospital the patient was discharged home to the care of her parents and was at that time quite unable to sit up.

Her general condition continued to deteriorate and she was referred to the Neurological Clinic of the Western Infirmary, Glasgow where she was seen, at 26 months, by Dr. J. B. Gaylor. At that time the parents felt that the patient could still see quite well and that she could understand what was said to her. Examination, then showed that her shoulders, as well as her legs, seemed to be spastic although her neck, arms and wrists were still flaccid. There was a bilateral extensor plantar response. On examination of the fundi the optic discs appeared to be a little pale but it could not definitely be said that the patient had optic atrophy. The maculae appeared to be normal^{and} as far as could be made out the child was not blind. Dr. Gaylor agreed that the probable diagnosis was 'encephalitis periaxialis diffusa' and kindly arranged for a psychiatric consultation also.

INITIAL PSYCHIATRIC CONSULTATION.

With the co-operation of Dr. Abramson facilities were provided for the child to be examined at Seafield Hospital, Ayr on 31st July 1956, when she was 26 months old.

At this stage the parents reported that although she had not spoken for two weeks (when she had last said 'Mamma' and 'Dadda') she still responded by smiles and laughs to their/

their approaches and by anticipatory movements to being picked up. When they showed the child objects she would seem to stare elsewhere but they felt, nevertheless, that she could see anything which was held up before her. They were even more strongly convinced that she understood all that was said to her - for example she would obey the injunction to put her arms round her father's neck. They had also noticed, at this stage, how she tended to grasp things and then to seem to be reluctant to relax her grip - moreover, everything she grasped was carried to her mouth and ^{she} was reluctant to let go with her teeth also. On the other hand she was so clumsy she sometimes dropped things she was holding and in the last few days the mother had found it necessary to fold the patient's fingers round a biscuit before she would hold it. In general, she had seemed, to them, to be rather more listless. For over a month she had had difficulty in feeding.

When examined, she was lying on her side in a cot in the opisthotonic position and seemed able to move about very little. The mother picked her up and nursed her on her lap and the child then showed a hypotonic posture, her head dropping forwards limply. At times however she could, and did, raise her head voluntarily but she would only support it for a short time. Her facial expression was dull and her mouth was open and drooling saliva. All her voluntary movements seemed to be poorly controlled. Yet she responded with smiles to her parents and took some interest in the doctor - the parents remarking that she was not afraid of him because he was not wearing a white coat. She was rather unhappy however, and/

and very easily upset. At no time during the examination did she make any attempt to speak.

General physical examination showed that there was no cough, cyanosis or lymphadenopathy and that the cardiovascular, respiratory and alimentary systems showed no abnormality. An attempt at a neurological examination was made. Although it was clear that the child was able to see and to fixate on various objects held before her, it was felt possible that there was some disturbance of peripheral vision despite the fact that the eyes would be attracted by objects brought in from the side. The eyes themselves showed some spontaneous and lateral nystagmus but the pupils were equal and reacted briskly to light. Her hearing seemed to be satisfactory and she lateralised sounds correctly. For 2 weeks she had been unable to lift her arms above her shoulders and her arms and wrists were flaccid and no tendon reflexes were elicited. Her hands were held in the en griffe position, the fingers being flexed at the inter phalangeal joints, and extended at the metacarpo-phalangeal joints. The thumbs were not held across the palms and there was some flexion and adduction at the wrists. During examination of the hands, she showed a grasp reflex on both sides and would also grope compulsively after any objects, such as the doctor's tendon hammer, which were made to touch her hands or which she saw near her hands. The legs were held crossed, the knees and ankles being extended. They were spastic, tone being high and the tendon jerks brisk. There was a bilateral extensor plantar response.

SUBSEQUENT PROGRESS. /

SUBSEQUENT PROGRESS.

During the following month she was living at home but her condition deteriorated gradually. She tried to speak at times but never succeeded. She laughed and smiled to her mother however. It was noticed that she would fix her eyes on something and her gaze could not be distracted. Her body became more pliable and flopped to the side more. It was noticed that for the last 2 months she had been biting more and that she seemed to enjoy doing it for she was always getting her rappy or her dress into her mouth and biting on it. On the other hand eating was more difficult, she was becoming unable to take solids or semisolids, choked quite frequently and had been fed by bottle. She was very constipated, cried for half an hour before defaecation and also had difficulty during the act. At this time she had an attack of tonsillitis which lasted for three days and during it she was upset and listless, had a temperature with sweating and was treated with penicillin.

When examined at the age of 2 years 3 months she seemed to respond intelligently to simple instructions:

- | | |
|-----------------------------|------------------------------------|
| Q. 'Hold your head up' | R. Patient did so with a smile. |
| Q. 'Laugh' | R. Patient did so |
| Q. 'Smile'. | R. Patient did so |
| Q. 'Mummy get your bottle?' | R. Patient responded with a smile. |

It was noticed also that she had a curious discolouration of the skin of the dorsum of the toes and feet. The mother herself pointed out that this looked like dirt/

dirt but that in fact it could not be washed off. In addition to previously noted physical signs it was found that when placed on her right side the grasp reflex was easily elicited in the upper hand but not in the lower hand. Lying on the left side a similar phenomenon was elicited although it was not quite so marked (Fulton, 1944).

It was following this examination that it was concluded that the clinical features resembled most closely those of the late infantile metachromatic leucoencephalopathic form of Schilder's disease.

TERMINAL STAGES.

During early September, 1955 (2 years 3 months) she had been having increasing difficulty in feeding and even swallowing fluids from a bottle was becoming difficult. She had been very constipated and had required daily suppositories. There had been considerable loss of weight. She developed a temperature and was readmitted to hospital on 5th September 1956.

On examination at that time it was recorded that her temperature was 101, pulse 146, respiration 36 and she was described as a pale miserable looking child who paid no attention when one spoke to or touched her. Breathing was audible in the throat and she whimpered a lot. The skin of the abdomen was lax and dry. She could not sit upright because she fell to the side and her head fell over her shoulder. Both hands had a claw like appearance although there was hypotonicity of the muscles and they straightened out readily - only to resume the claw position. There/

There appeared to be some spasticity of the upper arms which tended to be drawn across the chest. Legs were stiff and straight and tended to adopt a scissors position with the toes pointed down. Throat - there was moderate inflammation of the fauces with some tonsillar enlargement. No enlarged cervical glands. Ears - no evidence of any inflammation. Abdomen - No abnormal masses or evidence of tenderness. Cardiovascular System - No murmurs heard. Pulse regular 120/m. Respiratory system - coarse rhonchi heard throughout both lung fields. No moist sounds. Central Nervous System - Pupils reacted to light. There was no response when a pencil was moved in front of her eyes. Fundi - not seen as the child was restless. Reflexes - none obtained except plantars which were extensor. She appeared to be deaf.

Two days after admission she was examined again. Her legs were held in hyperextension and her elbows, wrists and fingers were flexed, the hands being held at shoulder level. She would usually follow objects with her eyes and would also turn her head towards a sound made in her ears. The pupils reacted normally but the fundi were not seen. Three weeks after admission a special ophthalmological examination indicated that the child was not blind and she followed movements of light and of hand purposefully and well. The pupils reacted normally and the fundi were normal although the discs were pale. Eye movements were full with occasional nystagmus. A further ophthalmic examination two weeks later showed little change - vision could not be assessed. At a special E.N.T. examination a few days later it was found very difficult to assess the degree of defect in hearing if any. The child rolled/

rolled her eyes when spoken to in an ordinary voice and she appeared to trace the source of the sound. She showed very definite pleasure by smiling and rolling the head when spoken to by a nurse whose voice she recognised. It was felt that the child might have a defect in hearing but not to any marked degree.

The patient died peacefully on 13th October, 1956 at 4.30 a.m. at the age of 2 years and almost 5 months, after an illness which had lasted for 20 months.

AUTOPSY FINDINGS.

External Appearances:- The body was that of a female child of appearance consistent with the age stated. There was no external evidence of disease or injury apart from the attitude of decerebrate rigidity with the lower limbs crossed and hyperextended and the upper limbs held flexed over the chest, with a claw position of the fingers.

Head and Neck. The cranial cavity, meninges, cerebral vessels, venous sinuses, middle ears and pituitary gland showed no abnormality. The thyroid (10 gm.) and thymus glands (10 gm.) were of normal size and consistence. The mouth, tongue and pharynx and salivary glands appeared normal.

Thorax. Both pleural cavities were dry and free of adhesions. The trachea and the major bronchi contained some fine froth. The lungs (each 120 gm.) were of normal size, shape, colour and aeration. There was no evidence of infection. The pericardium was normal and the heart (60 gm.) showed no evidence of acquired or congenital disease. The myocardium was of good quality. The sternal marrow was quite red.

Abdomen./

Abdomen. The peritoneal cavity was free of infection. The oesophagus, stomach, small intestine, appendix, caecum, colon and rectum were unexceptional. The liver was of average size, colour and consistence; the cut surface showed a normal pattern. The gall-bladder was empty. The spleen (35 gm.) showed slight prominence of the malpighian bodies. The pancreas (30 gm.) was unexceptional; the adrenals (together 8 gm.) were of normal shape, but the cortex, on section, was pale and narrower than normal. Apart from congestion the kidneys (right 50 gm. left 55 gm.) showed no significant abnormality. The ureters were normal; the bladder was empty. The uterus, tubes and ovaries appeared normal. The lymph nodes of the abdomen, thorax and neck were rather larger than usual.

General Histopathology.

Liver - well preserved; mild congestion: some small round cell aggregates: occasional eosinophils in the sinusoids. Spleen: Some reactive change in lymphoid in pulp. Kidney: Acute congestion. Pancreas: Normal parenchyma: islets a little larger than normal in some instances. Thymus: some eosinophils were noted both in lymphoid tissue and trabeculae. Heart: Appearances were unexceptional. Lung: Patchy collapse with polymorphs present in interstitium but no evidence of bronchopneumonia. There were lymphocytic foci adjacent to some bronchi. Fairly marked congestion and some patchy oedema at the bases. Thyroid: some variation in acinar size. Adrenals: Small, but well defined. Zona glomerulosa and medullary layers. Frozen-section showed good lipid content. Pituitary: Differentiation of anterior cell types was good: no/

no abnormality. Ovary: Apparent follicular activity. Vagina and cervix: Some round-cell infiltrates in the submucosa. Endocervix was very long and there was an apparent septum in the lower portion of the uterine cavity, the upper end of which was rather dilated. Lymph nodes: These showed some reactive hyperplasia. Salivary gland: This appeared normal. Trachea; showed no evidence of infection. Gallbladders: The mucosa was rather thick and polypoidal. Some round cell infiltrates were present in the substance of the wall. Stomach, Small Intestine and Colon: Were unexceptional. Bladder: Showed no evidence of significant infection. Sternal marrow: This was well preserved and showed no abnormality. Skin: showed no abnormality. Aorta and Brachial artery; appeared normal. Tongue; showed no abnormality. Gluteus maximus, Pectoral and Rectus muscles: showed no significant change. Neuro-muscular spindles were well seen.

Central Nervous System.

Gross inspection. The brain was of average size for this age (weight -1050 gm.) and showed no gross variation in gyral size, no flattening of surface convolutions and no coning of the cerebellum. There was a suggestion of falling in of the cortex over Broca's area on each side. The spinal cord was dissected out and macroscopically appeared normal as did the optic, brachial and sciatic nerves. The posterior part of one eye was removed and appeared normal.

Primary Section.

Primary Section. - This was avoided with a view to carrying out special studies.

Neurohistopathology.

Cerebral hemispheres - sections taken from widely separated areas showed similar appearances which were consistent in many blocks. There was no cuffing of the blood vessels and the features were of a chronic demyelinating process affecting the white matter only and not producing marked gliosis the process having proceeded to an extreme degree presumably because death had been long delayed by the administration of antibiotics. The white matter was, on the whole, poorly cellular, presenting a rather granular fibrillary appearance. Scattered throughout, were large microglial cells many of which had lost their nuclei. They were of pink colour in a haemalum and eosin section but stain brightened by the P.A.S. method. They also stained metachromatically with the conventional dyes. The appearances were those of the diffuse metachromatic leucoencephalopathic variant of Schilder's disease.

Cerebellum - Similar changes to those in the cerebral hemispheres were found.

Eye and Optic Nerve. The sclera, choroid and retina appeared normal and there were no myelinated fibres present in the retina. The optic nerves showed no gross evidence of demyelination. The pattern was, however, rather blurred on transverse section, there was some vacuolation apparent, nuclei appeared to be vaguely defined or absent, and the myelin sheaths were blurred and ill-defined. Some of these changes may have been artefacts but histiocytes containing P.A.S. positive material was present.

Medulla and Spinal cord. - There was severe demyelination of the fibres of the pyramids and of the cortico-spinal tracts in the lateral columns. The fibres of the reticulo-spinal tracts in the lateral columns anterior to the cortico-spinal tracts were partly demyelinated but much less severely so.

Brachial and Sciatic nerves - These showed no gross change although the latter, in longitudinal section, showed some globule formation in Loyez stained sections.

Fig.6. Serial photographs of Mary S. at different ages showing development of initial hypotonicity and later spasticity.



(a) Eight days



(b) Eleven months



(c) Eleven months



(d) One year



(e) 2 years - child unable to walk. Note position of fingers.



(f) 2 years 2 months. Note clawing of fingers. Child unable to raise arms higher.



(g) Two years three months. Note hypotonicity of trunk and neck with spastic crossing of the legs and clawing of fingers. Other child of identical age for comparison.



(h) Two years three months. Note 'scissor' gait and hypotonicity of facial muscle.



(i) Two years four months (shortly before death). Note forearms flexed over the chest.

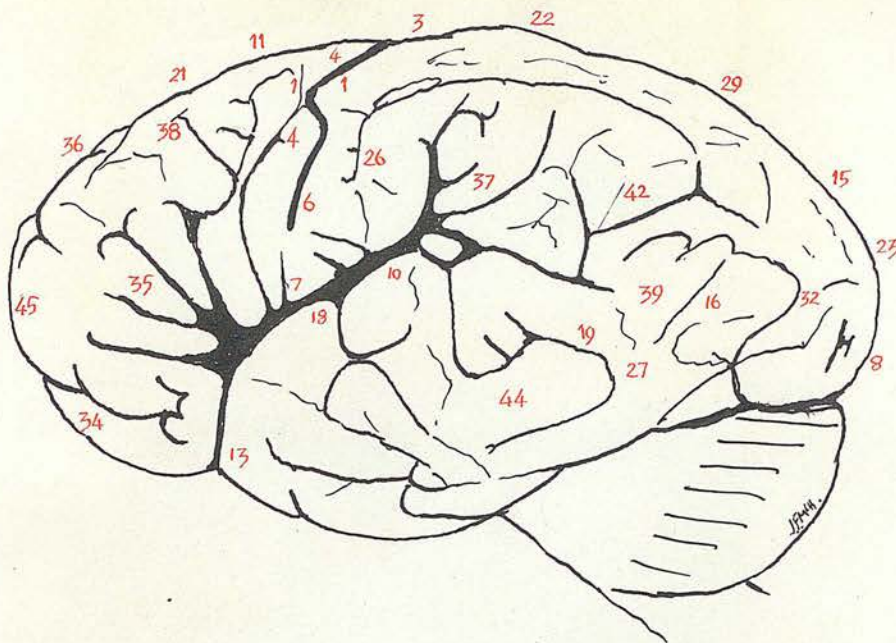


Fig. 7. Drawing of the brain in Case 1 which was used for identification and labelling of Flechsig's myelinogenetic zones. The sites of the figures indicate the sites of the blocks taken. In the actual event, the stage of demyelination was the same in all areas.

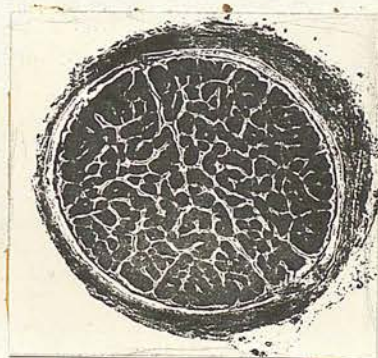


Fig.8. Optic nerve to show absence of marked change in myelin (although the Periodic Acid Schiff method of staining showed histiocytes containing P.A.S. positive material). Loyez Stain. X 12.

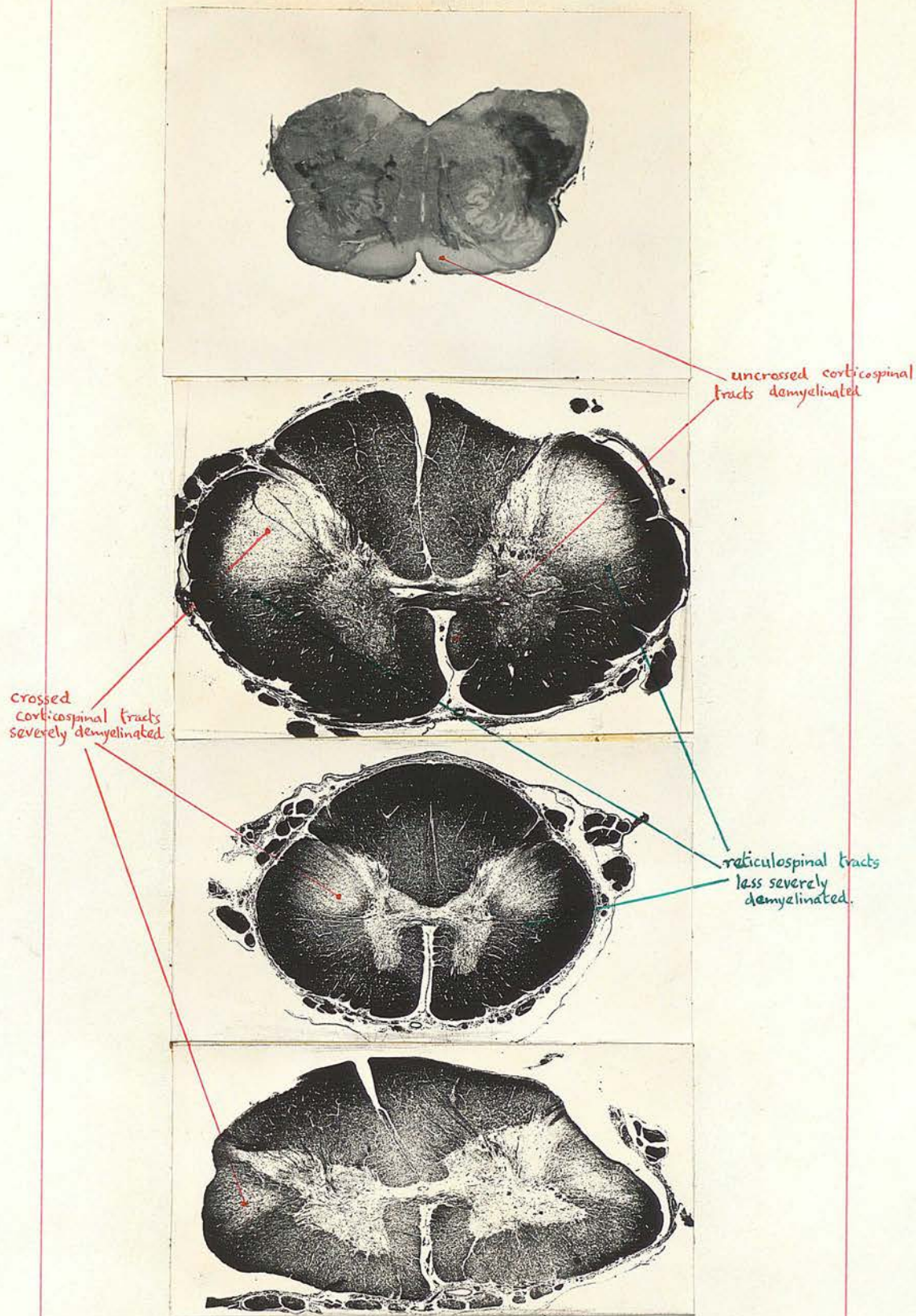
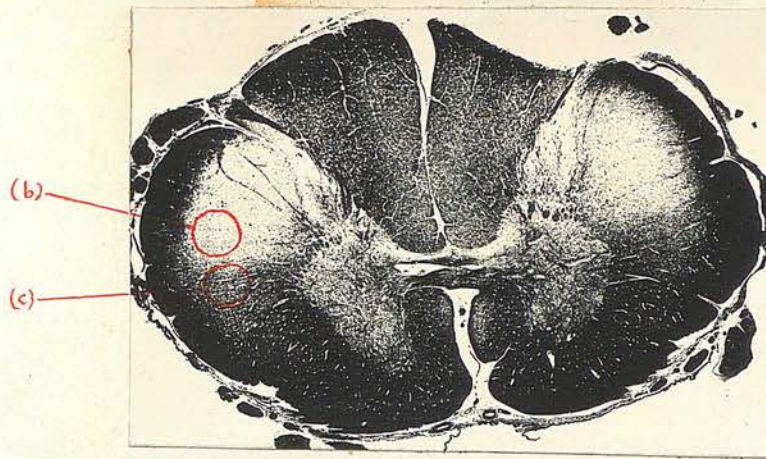


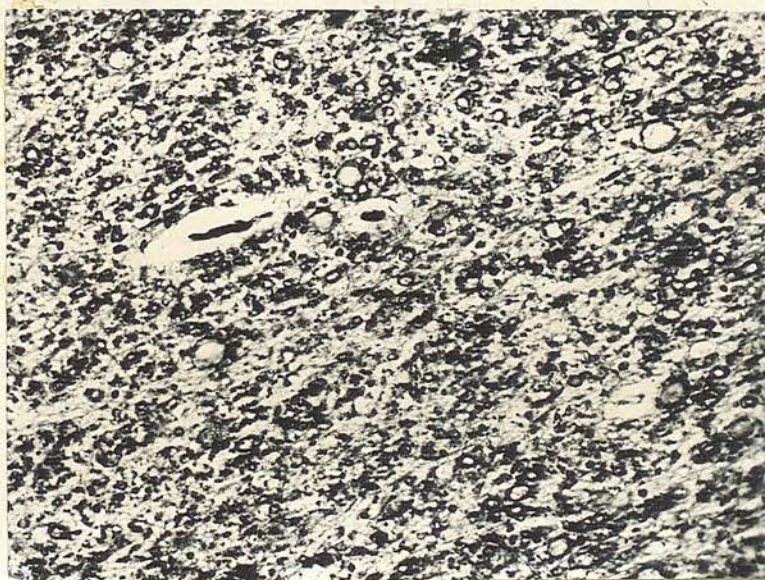
Fig. 9. Medulla oblongata and spinal cord to show demyelination of the cortico-spinal tracts and, to a lesser degree, of the reticulo-spinal tracts. Loyez. X 8.



- (a) Low power, to indicate sites of the high power fields below and the relative involvement of the corticospinal and reticulospinal tracts.



- (b) Corticospinal tract showing an advanced degree of demyelination with loss of many myelin sheaths. Only occasional distended sheaths remain.



- (c) Reticulospinal tract showing early degenerative change with some swelling of myelin sheaths; demyelination is, however, minimal

Fig.10. The relative involvement of the corticospinal and reticulospinal tracts in the cervical cord.

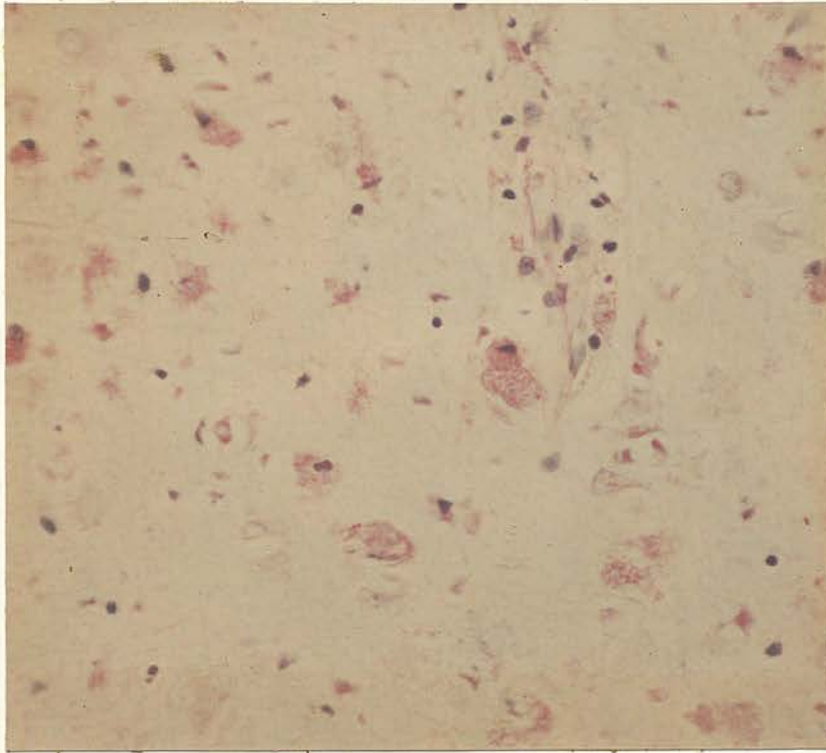


Fig.11. Colour photograph to show the metachromatic material in the white matter (Periodic Acid Schiff)

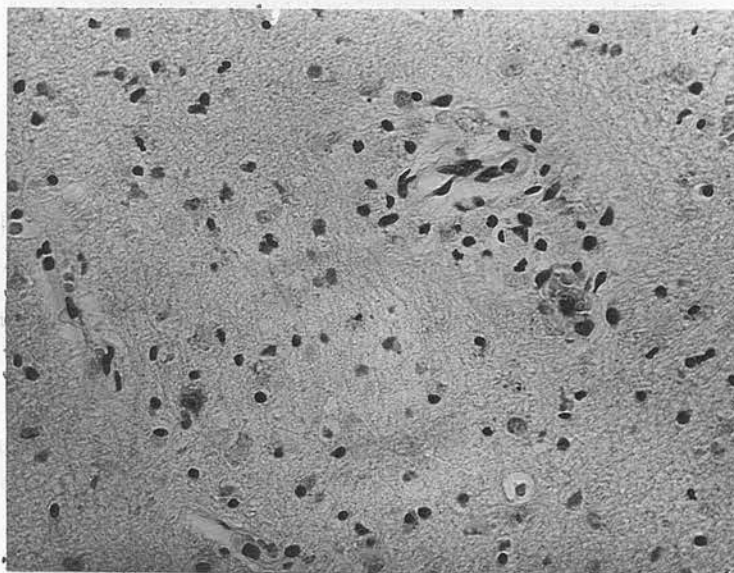


Fig.12 Parietal region to show viable nuclei around blood vessel. Gitter cells and metachromatic material are seen in the white matter. Haemalum & Eosin X 310.

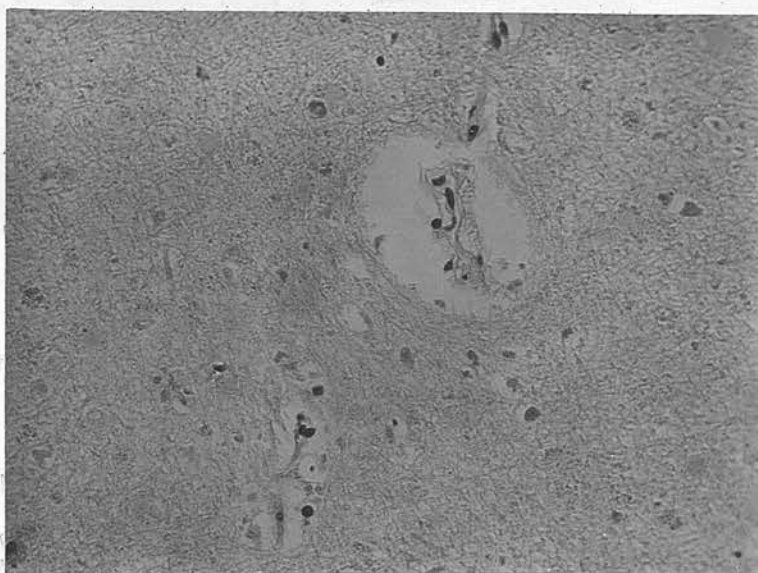


Fig. 13 Prefrontal region to show complete demyelination of white matter and scattered deposits of metachromatic material. Occasional nuclei are seen especially associated with blood vessels. H. & E. X 310.

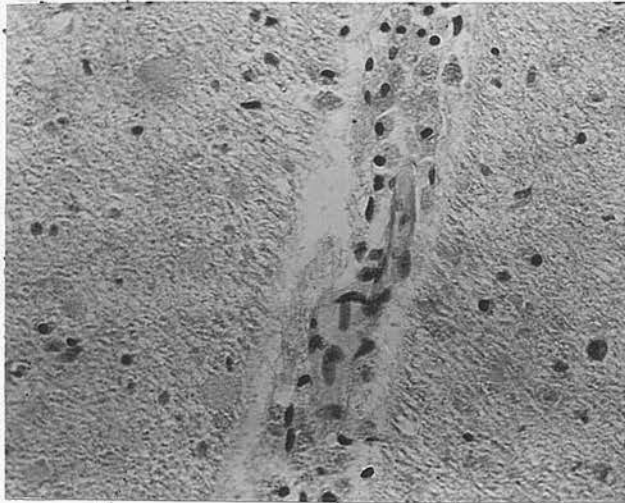


Fig.14 Precentral gyrus to show similar appearance although here some gitter cells are seen in a perivascular position. H.E. X 310.

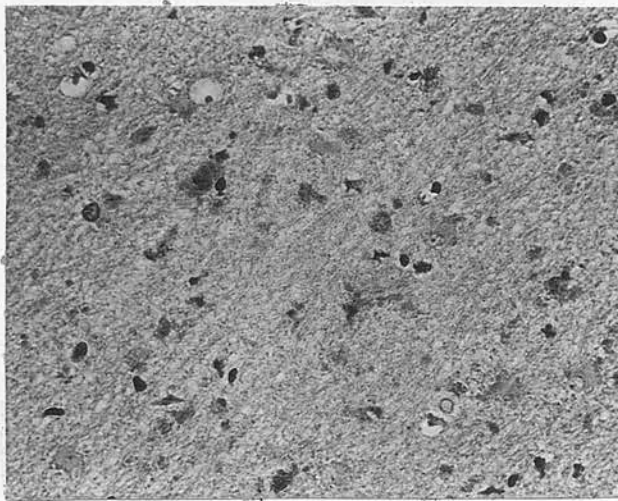


Fig.15 Inferior frontal gyrus to show demyelination and rather abundant metachromatic masses scattered throughout the white matter. H.E. X 310

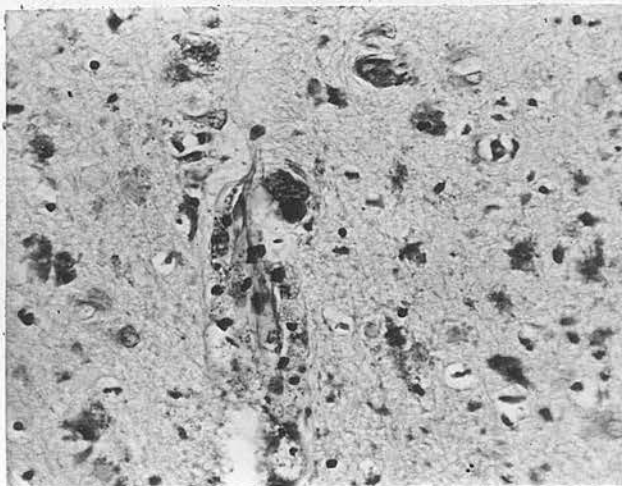


Fig.16. Same region to show metachromatic material stained by Periodic-acid Schiff technique. This material is also stainable in frozen sections by other suitable metachromatic methods. X 310.

CASE 2. A YOUNG SCHOOL BOY.WILLIAM N. (died aged 8 $\frac{8}{12}$)Presenting feature - Deterioration in hearing.ANAMNESIS.

The details of the history were obtained from the parents, from school teachers and from others in contact with the child and were pieced together into chronological order during the course of several interviews.

Family History.

Father - alive and well but had a slight divergent squint. He was one of a family of four including one set of twins and one of his siblings died aged 14 of "stoppage of the bowel". Paternal Grandfather - alive and healthy. Paternal Grandmother - died, aged 43, of diabetes.

Mother - alive and well. She was one of a family of ten, four of whom were dead. One died of bronchitis, one (a twin) died at birth. The mother could not recollect the causes of the deaths of the other two. Before the patient's birth the mother had been well throughout the pregnancy. Maternal Grandparents - both alive and well.

Siblings - (1) Patient, aet 8; (2) Sister, aet 6 - she had a hare lip and cleft palate and still suffered from enuresis; (3) Brother, aet 1 - appeared to be healthy.

There was no history of mental illness in the family.

Personal History.

The patient was born at home after a full-time spontaneous labour on 19th August, 1945. His birth weight was 10 lbs. and he was a lively baby. He was bottle-fed and/

and mixed feeding was started at four months. He was bright and active and laughed a great deal.

He sat up at six months and walked at one year. Speech development was normal. The family lived with the mother's parents until he was four, when they moved into a "prefab". At the age of five Billy went to the primary school where he was an average scholar. He moved to his secondary school when he was 7 years 6 months.

Previous Personality:

The patient had shown no special nervous traits in infancy or early childhood and had been looked upon by his parents and teachers as being normal mentally and physically up to the time when he went to his secondary school. He was described as having been, before his illness, an obedient, friendly and good-tempered little boy. Though not pugnacious, he had been looked upon as a leader at the primary school.

Previous Health.

He had chickenpox at the age of 10 weeks and measles at the age of 2. At the age of 5 routine medical examinations at school, including tests for vision and hearing, had all been normal.

Present Illness.

The onset of the illness had been noticed at about the age of 6 but had been extremely insidious. The one and only symptom at that stage was a slowness and difficulty in learning to read. It was noticed in particular that the boy persisted longer than his class mates in having to enunciate words aloud before being able to grasp the meaning of the text. Although this slowness and difficulty in learning to/

to read was sufficiently marked to be distinctive, in comparison with the ability of the other children in his class, it was not looked upon as being grossly abnormal and the boy, who was otherwise intelligent, was merely looked upon as being a 'backward reader'. Indeed it was only because the continuing difficulty in learning to read merged into an actual inability to read that it was felt justifiable to regard it as the earliest clinical manifestation of the disease. During this early stage, despite the difficulty in learning to read, the patient had continued to make active and steady intellectual progress as indicated by his school work.

It was not until the boy was 7 years 5 months that symptoms additional to the difficulty in learning to read began to appear. He began to have unexplained tearful attacks and the parents were puzzled because, whereas previously he had been looked upon as a leader, he seemed, then, to become the butt of his schoolmates and to become noticeably less stable emotionally. At first the changes were put down to the change to the secondary school. His new teacher noticed his 'sensitiveness' also, but not having known him previously, regarded him merely as being a naturally shy and retiring child. This temperamental disturbance developed very slowly, however, so that it was not until many months afterwards, when irritability, emotional instability, vindictiveness and lack of self control had become obvious, that the parents were able to look back and to date the onset of the emotional change.

Despite early emotional symptoms intellectual changes were on the other hand not at first in evidence. At the age of/

of 7 years 6 months at the time of leaving the infant school he was assessed by routine educational tests as "average" (Grade C) in all subjects. Even at 7 years 7 months his writing and drawing were found, on retrospective investigation, to have been up to normal standard (see Fig. 18b) and in some other subjects (especially arithmetic) he had been described by his headmaster as a little above average although his reading difficulty continued. This was noticed particularly in reading the blackboard, and the teacher formed the impression that it was due to lack of attention. Nevertheless, despite his slowness, the boy was in fact making steady and definite progress in his reading ability. However, at 7 years 8 months there was, for the first time, a falling off in his general school work which, like the emotional change, was at first very slight and was noticed first by the teacher only in an unexpected difficulty with sums. By the following month his grading at school, by routine tests, had fallen off slightly in all subjects so that he was then "below average" (Grade D). Although from that time onwards there certainly appeared to have been a more definite and progressive intellectual deterioration it must be emphasised that this was not at all obvious until many months later, and was probably due, largely, to the development of certain defects of a specific nature.

The first of these specific defects was a transformation of the difficulty in learning to read into an actual inability to read, at 7 years 10 months. During the preceding term Billy's reading ability had improved and had in fact reached its zenith so that when the holidays started/

started he had been taking an interest, at home, both in reading a newspaper cartoon known as "Oor Wullie" and in reading spontaneously the general newspaper headlines. Having reached this level his parents were then naturally disappointed (and surprised) to see him rather rapidly lose this slowly acquired faculty. They first noticed that, when attempting to read a book, he would hold it very close to his face and attempt to read from the end of the bottom line on the right hand side of the page (visual inattention to the left, a trait which he had not shown previously) and shortly after that he became quite unable to read at all. The parents noted also that he himself never complained of his inability to read and he therefore gave the impression of deliberately avoiding making any effort to read, especially ^{when} encouraged to do so. For this reason they had felt convinced that he could probably still read quite well if only he would put his mind to it and they had not therefore been greatly concerned about this symptom.

Difficulty in writing and spelling developed at about the same time (7 years 10 months) and his parents noticed specifically that in writing his name, which he had been able to do correctly for some time, he could 'get no further than the first 'i' in 'William' '. Nevertheless they felt from his general behaviour that his actual vision at that time was unimpaired partly because he never complained about his eyesight but particularly because he always spoke quite normally about objects he was looking at or playing with (such as pictures and toys) and was able to handle them without difficulty).

At the same age (7 years 10 months) there appeared, also, the very earliest, and only slight, signs of occasional difficulty in understanding what was said to him, a difficulty which was later interpreted by the parents as 'deafness'. In the middle of the month, at a school picnic Billy, who had always been a good runner, had seemed not to respond to the starting signal for a race and his slowness off the mark had been commented on by friends. His mother in fact looked upon this occurrence as being the first indication of his hearing being abnormal. Towards the end of the month she began to feel that he was not always paying attention to what was being said, because sometimes he ignored remarks made to him. Yet, at other times, he seemed to hear quite well when spoken to, even in an ordinary voice. Because of this variability his mother felt she could reassure herself that there could be nothing seriously wrong with the boy's hearing. Indeed she came to the conclusion that he was pretending not to hear and she got into the habit of addressing him sharply, even shouting at him. He responded to this approach by beseeching her not to shout because the noise frightened him and this response further convinced the mother that her boy was not really 'deaf'. As his apparent 'deafness' nevertheless persisted, he was taken at 7 years 11 months to see the family doctor, when the ears were found to be healthy.

It was on the way to the doctor's surgery it was noticed that the boy occasionally bumped into lamp posts and this was the first clear indication of a peripheral visual field disturbance to one side, or at least of a visuospatial disturbance or visual inattention to that side./

side. Unfortunately the father could not remember for certain on which side the collisions had tended to occur - but probably it was on the left. It was also at this stage that the changes, already noted, in his temperament were becoming rather more marked. He was more easily distracted from one type of occupation to another, more self-centred and apt to cry if he did not get what he wanted. He was more restless, impatient, bad tempered, irritable and even spiteful with his younger sister and the baby. It was these features which lent plausibility to the psychogenic theory of his illness which had to be considered at the time of his referral to the psychiatric clinic. It was noticed at that time also that he occasionally was unsteady on his feet and once he grazed his head slightly falling off a "joy wheel" in the park. Indeed, for a short time after that accident he had had difficulty in balancing to such an extent that he had not at times been able to walk properly without help. This was only a transitory disturbance and cleared up quickly so that he was once more able to walk about by himself quite normally. After that accident it was noticed that he seemed never to look down to see where he was putting his feet with the result that he was always tripping over stones or pieces of wood yet steady in his gait on an ordinary floor. Nor would he look out for approaching traffic when crossing the road. At the age of 8 his mother noticed specifically for the first time that he sometimes seemed to grope for door knobs and light switches if they were on the left side. Towards the end of the same month he had more frequent unexplained crying fits and his 'deafness' deteriorated. On return to school/

school, he was promoted to a new class but the new teacher noticed immediately that there was something wrong with him. She also presumed him to be deaf as he did not obey simple orders such as to sit down on a particular bench. She was particularly puzzled because he did not obey even when the bench was pointed out to him by gesture.

After two days back at school he had his appointment at the E.N.T. Hospital. When he was examined there enlarged tonsils and adenoids with cervical adenitis were found and, although there was no evidence of middle ear infection, it was thought that tonsillectomy might relieve his 'deafness'. He was admitted to an E.N.T. hospital at the age of 8 years 1 month for tonsillectomy to be performed. The impression then was that his hearing had deteriorated but his responses to hearing tests were considered to be unreliable and he had a fatuous grin which gave the impression that he was mentally backward. A skull- X-ray was negative but as he had a tendency to stagger, the proposed tonsillectomy was not carried out and a neurological appointment was arranged. On returning home from the E.N.T. hospital he complained, for the first time, of headaches. These were to recur but were never, the mother insisted, at all constant or severe. He was subject, also, to more frequent crying fits, which lasted a longer time and in which he seemed to be angry and impatient rather than unhappy or in pain. His mother formed the impression that the 'deafness' was always worse after these attacks. He also became more 'disobedient' but again she herself thought that this was really due to him not understanding the verbal orders which were being given to him.

It was not until September 1955, at the age of 8 years 1 month, that spontaneous expressive speech showed for the first time, a slight change. This was manifest in three respects. Firstly, he lost emotional control over his tongue in the sense that he started to use 'terrible swear words, words he had never used before' and quite out of keeping with his normal manner, and his mother was particularly disturbed because he seemed to have no sense of shame about using them. Secondly, there was a slight change in his actual manner of speaking which the parents were emphatic did not constitute a stammer - it was more as if his speaking had become "slowed down". Thirdly, there were some very slight paraphasic symptoms although these were only elicited after very careful questioning of the parents. They had in fact noticed him, from time to time, using an inappropriate word or expression. The father explained this as follows:- "I've seen him make a mistake and then correct himself. Once he said he had been to see a film of "Lobbel and Hardy" (Laurel and Hardy), but he immediately corrected himself and got it right". Similarly, the father had been struck, on another occasion, by the boy using a totally inappropriate word (which unfortunately the father could not recall) and then remarking irritably "it's no' that, Daddy, it's - ", correcting himself and using the appropriate word.

He attended a neurological clinic for investigation of his 'deafness' as arranged at the E.N.T. hospital but no neurological cause for his deafness was discovered. His alexia was not mentioned by the parents nor was it elicited/

elicited during examination but examination of the fundi and tests of vision then and on several subsequent occasions did not reveal any visual abnormality or field defect. It was as a probable case of hysterical deafness that he was referred to the psychiatric clinic of the Western Infirmary, Glasgow.

INITIAL PSYCHIATRIC STUDIES.

The patient first attended the psychiatric clinic at the age of 8 years 1 month. He himself did not spontaneously formulate any specific complaints and it was confirmed that physically, there were no abnormal signs. Indeed after the first superficial investigation it was not difficult to formulate a tentative psychogenic hypothesis for his supposed hysterical deafness in terms of sibling rivalry, maladjustment at school with a new teacher and so on. Nevertheless, a closer study (*vide infra*) of the hearing difficulty itself, even at the first interview, was sufficient to suggest strongly the probability of an organic dysphasic disturbance. Because of this a more detailed enquiry into the personal history, as already described, was instituted and at the same time more detailed clinical studies of the patient himself were embarked upon. The patient was examined and observed directly, closely and repeatedly not only at the clinic but in the natural environment of his own home. All this was done during that period of the illness before the appearance of any objective physical signs whatever. The continued absence of such signs was confirmed by repeated neurological examinations, including re-referral to the neurological/

neurological clinic.

General Observations.

In his general attitude and mood he was at all times cheerful and friendly and the emotional changes, although already evident to the parents, were not such as to be detected in the interview situation at this stage particularly as he always seemed pleased to see the doctor.

His spontaneous behaviour was studied in the clinic, but more revealingly during visits to his home and garden when he was seen to be very active, yet rather clumsy in all that he did. He fumbled when trying to tie a knot with string and could make nothing of it at all. He stumbled and fell quite often - apparently not because of unsteadiness, but as a result of tripping over objects he did not seem to notice visually. Despite these falls he continued undaunted in his play. At the clinic he was conscientiously co-operative in carrying out tests (within the important limitation of his difficulty in understanding spoken speech) and indeed he seemed to take considerable interest in the specific tests which were set him. Because his understanding of questions and instructions was unreliable there were many formal tests which it was impossible to administer. In fact it was frequently necessary to resort to improvised techniques, especially in testing the visual fields, in which spoken speech was eliminated as much as possible. In particular, of course, verbal intelligence tests were out of the question.

When addressed he would come up to one and stand very closely indeed looking up into one's face with a broad grin.

He/

He invariably stood so close as to be touching the examiner so that the impression was that he had difficulty in estimating distance visually and that only by being in actual contact could he know he had reached the person addressing him. His general ability to deal with other visuo-spatial problems was observed, in a preliminary way, by watching his spontaneous play. At home this consisted mainly of constructing a hut in the garden with sheets of corrugated iron and there was no evidence of three dimensional constructional apraxia as he did this although, having completed the task, he repeatedly pulled the hut down and rebuilt it. His parents said that this game had been carried on with some zest for several days and it was felt therefore that the repetitive activity of building up and pulling down could represent a reassuring defence against an incipient failure of constructional ability.

Hearing:- At the first interview, although the patient spoke clearly, grammatically and intelligently, one was struck by his poor understanding of spoken speech. This was so widely variable that the immediate impression was of an auditory dysphasia rather than a true deafness. He did not appear to be lip reading. Because of this impression, before embarking on a more detailed study, a preliminary, but unsuccessful, attempt was made by jingling keys (out of sight) and by holding a ticking watch near to his ears to assess whether he had an auditory agnosia. He was encouraged to describe what he heard, but probably did not understand the verbal instructions. He listened with interest, but unfortunately he did not describe spontaneously the nature of the sounds he heard so that it was really not possible to elicit the presence or absence of auditory agnosia.

The question of an auditory aphasia was then considered. In conversation he appeared sometimes to understand perfectly well questions spoken in an ordinary, or even in a deliberately quiet, conversational voice although at other times his response indicated a complete misunderstanding of the question strikingly associated with an apparent confidence on his part that he had, in fact, understood. Several times, in response to various questions, the boy did not reply but opened his mouth very widely as if he had the impression that the doctor was saying "Open your mouth" - a request he must have had frequently from other doctors, and one which no doubt he was always expecting. The following conversation at his first interview suggested a receptive dysphasia. It was carried out using a quiet voice, the examiner being careful to speak very distinctly and to avoid using significant gestures of any kind or hinting whether the patient had replied incorrectly or irrelevantly:-

Q. "How are you?"

A. "Fine".

Q. "What's been wrong?"

A. "Coming up for nine". (The patient assumed he was being asked his age)

Q. "Where do you live?"

A. "At Carmyle prefabs". (Correct)

Q. "How old are you?"

A. "Eight"

Q. "Do you go to school?"

A. "No. Not till my ear's better" (Correct)

Q. "What's been wrong with your ear?"

A. (Pointing to his left ear) "This one". (The patient did not grasp the question accurately).

Q. "What happened?"

A. "Till my ear's better". (An irrelevant reply)

Q. "What happened?"

A. "Fell off the joy wheel at the swings". (The repeated question was grasped this time)

Q. "Will you stand up?"

A. "....myle prefabs". (Again an irrelevant response)

Q. "Hold up your hands"

A. (Patient held up only the right hand).

Q. "Will you stand up?"

A. "Yes". (But he remained seated)

At another examination within a few days of his first attendance he responded to a hand-clap near his ear from behind but did not seem to be able to localise the origin of the sound. This was shown also by the fact that when he was called to across the room he looked round at the various people present but was clearly not able to tell from which direction he was being called. During a visit of the psychiatric social worker to the home it had been noticed that he had not responded readily to her conversation but that he understood his mother's questions fairly easily. On another occasion at his own house (when he was, as usual, very attentive and co-operative) his auditory dysphasia was confirmed by further conversation with the doctor:-

Q. "How are you feeling?" (The question had to be repeated several times)

A. "Yes". (Patient nodded his head and had obviously not grasped the question).

Q. "Do you know me? Who am I?"

A. "You're the doctor....."

Q. "Do you understand what I say?"

- A. "Yes".
- Q. "Put out your tongue".
- A. (The patient did so correctly)
- Q. "Hold up your hand".
- A. (The patient merely smiled broadly)
- Q. "Do you understand that?"
- A. "No".
- Q. "Hold up your hand"
- A. (After some thought, the patient put out his tongue and then held his hand forward)
- Q. "Can you touch your ear?"
- A. (The patient again smiled broadly)
- Q. "Let me see you touch your ear".
- A. (With the tip of his right index finger the patient touched the top of his head).
- Q. "Can you stand up?"
- A. "Yes". (The patient remained seated).
- Q. "Let me see you stand up"
- A. (The patient did so)
- Q. "Now sit down".
- A. (The patient did so)
- Q. "What's that?"
- A. "Pen" (Correct)
- Q. "Do you know what a bicycle is?"
- A. "We've got a three wheeler".
- Q. "Will you draw a bicycle?". (Examiner put pencil and paper before the patient)
- A. "Yes, I've tried but it falls". (Again irrelevant to the question but relevant to his own line of thought).
- Q. "Will you draw?" (The question was accompanied by appropriate gestures by the doctor).
- A. (No response)
- Q. "Will you draw a bicycle?"

- A. "A three-wheeler; I can go a two-wheeler a bit".
(There was some perseveration, with inattention to the actual question and no move to attempt to draw)
- Q. "You draw! "
- A. "Yes" (But he still made no attempt to do so)
- Q. "Draw on the paper"
- A. "No". (The examiner then held the pencil to the patient's hand). "I canna' draw".
- Q. "Do you know what a daisy is?"
- A. "No".
- Q. "Do you know what a flower is?"
- A. The patient uttered a word which sounded like "petals" and then said "bees" in a firm voice.
- Q. "Draw a flower"
- A. "I couldnae"
- Q. "What did you get for Christmas?"
- A. "That's the wean greetin' in his bed....." (This was taken as an indication that the patient was fatigued and losing interest so the interview was brought to a close)
- Q. "Go to the door".
- A. "Yes". (The patient made no move)
- Q. "Go to the door". (The examiner made appropriate gestures).
- A. "Down there?". (The patient walked to the door and back. He then spontaneously went out at the door, visited the bathroom and returned)
- Q. "Go and play.....off you go.....go into the gardengo and build your den".
- A. The patient sat smiling comprehending none of these successive commands. Finally he held up his hand in the obvious hope that he was responding correctly.

Vision. There had been a suggestion from the history of a visual field disturbance to the left. This had not been verified at the neurological clinic but at the psychiatric clinic, although there was certainly no complete homianopia, /

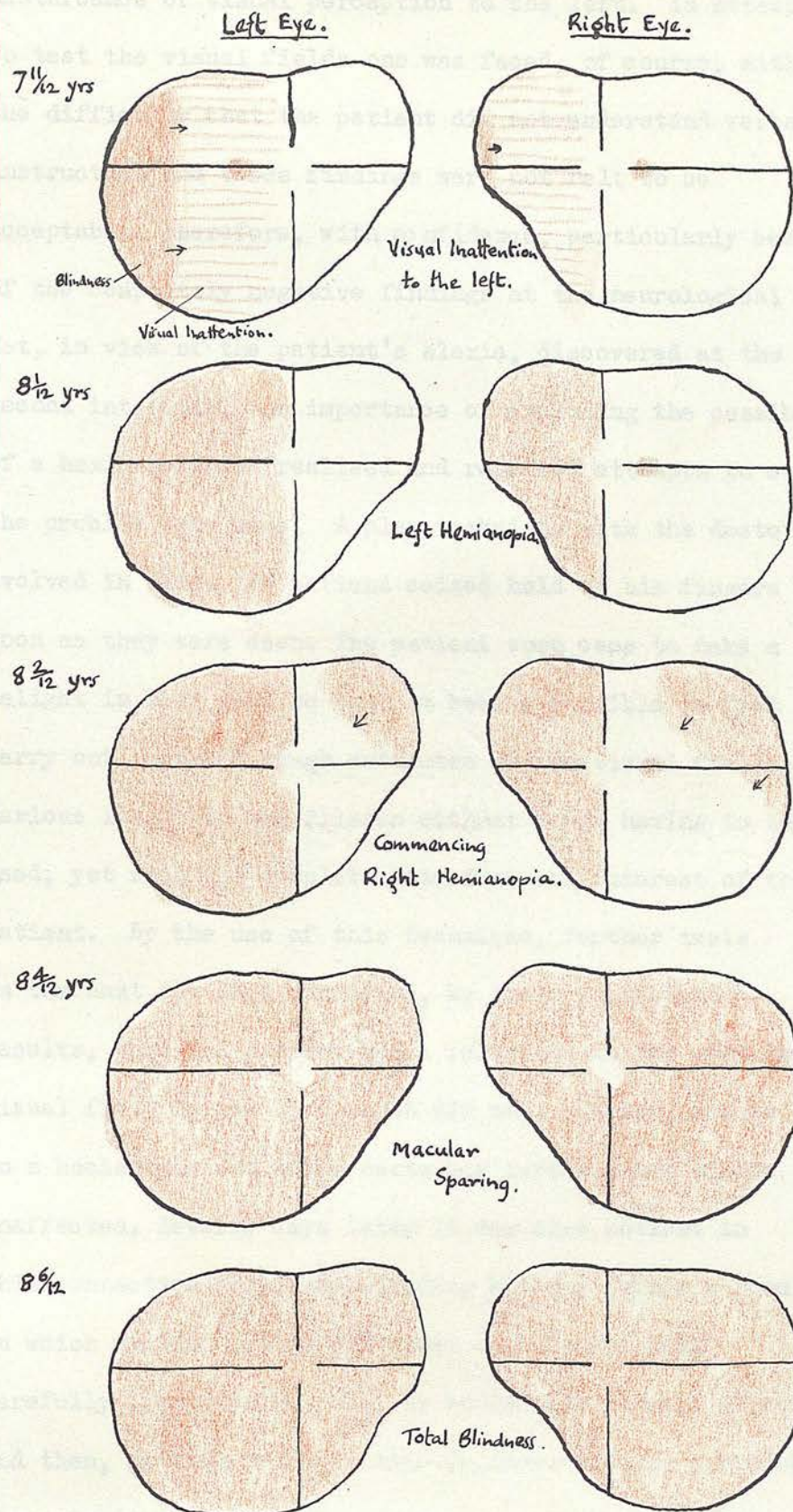


Fig. 17. Diagram illustrating the visual field changes in Case 2 (the schoolboy)

hemianopia, the impression was that there was a peripheral disturbance of visual perception to the left. In attempting to test the visual fields one was faced, of course, with the difficulty that the patient did not understand verbal instruction and these findings were not felt to be acceptable, therefore, with confidence, particularly because of the completely negative findings at the neurological clinic. Yet, in view of the patient's alexia, discovered at the second interview, the importance of excluding the possibility of a hemianopia was realised and repeated attempts to solve the problem were made. A play technique with the doctor was evolved in which the patient seized hold of his fingers as soon as they were seen. The patient soon came to take a gleeful delight in this game so that it became possible in fact to carry out repeated rough estimates of the visual fields at various stages in the illness without words having to be used, yet with the complete attention and interest of the patient. By the use of this technique, further tests in the next few days confirmed, by their consistent results, that the patient had a reduction in the peripheral visual field on the left which did not, however, amount to a hemianopia and which certainly left macular vision unaffected. Several days later it was also noticed in this connection that, when finding his way across a room in which various chairs and other objects had been carefully placed in his way, he would halt at each object and then, getting round it with deliberation, he invariably chose to go to the right.

His central vision was satisfactory and he had no difficulty whatever with the visual recognition of objects.

He/

He was able, for example, to recognise on sight the doctor himself and to name correctly objects presented to him individually (e.g. a bowl of goldfish, a halfpenny, a shilling, three shilling pieces seen together, a pen, matches). It was interesting, however, that he had difficulty in enumerating a group of objects presented together. Two pennies, a halfpenny, a shilling, a ring and a pencil had been put before him in a group and he had been asked to pick up the halfpenny or to touch the halfpenny. He did not respond appropriately to these spoken instructions, presumably because of his auditory disability, but, without touching the objects, he spontaneously enumerated them as follows:- "two shillings and a shilling and a penny and another penny and another halfpenny and a halfpenny". Thus he did not order the objects systematically - omitting some and enumerating others more than once.

Reading: Although central vision was intact and there was no visual object agnosia it was at the second interview that it was discovered that his ability to read was severely affected and it was then that the history of dyslexia-alexia was obtained. He was given some simple printed words as a test but although he tried hard he could not read any of them. He could not, for example, read the word "cat". In spite of this, a few moments later, when presented with his surname "NISBET" he said, fortuitously introducing his Christian name, "William Nisbet". He was therefore presented with his full name "WILLIAM NISBET", but he was not able to read it at all this time and merely said "I couldnae write (sic) that".

Writing: On the same occasion attempts were also made to get him/

Fig. 18 Tracings showing deterioration
in writing.

(a) Aged 7 years 7 months:-

1 I red was seven
years old.
2 I de hed two sister

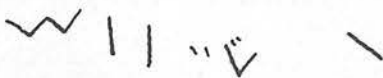
(b) Aged 7 years 9 months:-

William J. Nisbet

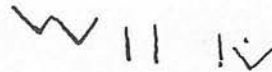
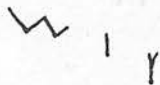
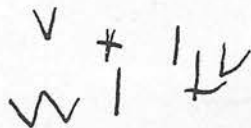
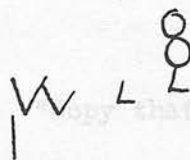
(c) Aged 8 years 2 months:-

(a) Write your name (a little later):-

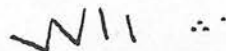
"Write your name"



"Write your name, write William Nisbet".

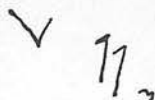
WILLIAM NISBET



"Copy that:-"

(b) Copying and drawing.

WILLIAM NISBET



(d) Aged 8 years 2 months (a little later):-

"Write your name, write William Nisbet".

m n 1 1 1 1

"Copy that:-"

WILLIAM NISBET

7. 1. 7.

(e) Copying and drawing.



cat



(a clock face).



him to write, beginning with his name. He made repeated painstaking efforts to do so but with little success. He was also asked to copy his name "WILLIAM NISBET" but again with little success. A few days later his response to requests to write and to copy his name followed a different general pattern but were equally unsuccessful. It is noteworthy that his efforts to write his name repeatedly followed the same mistaken pattern and were not random scrawls (see Fig. 18). Attempts to get him to write down figures to dictation were also unsuccessful:-

Q. "Write down 'two'".

A. "No".

Q. "Write down 'three'".

A. The patient painstakingly drew a little sketch which the doctor took to be a 'tree'.

Speech: As the patient was usually a little shy during interviews, there was not always very much spontaneous speech, but it was normal in form. Occasionally, indeed, he had bursts of enthusiastic conversation, perhaps about his rabbits or his other childhood interests and at these times his speech was noticed always to be perfectly clear and grammatical. For example, during a visit by the psychiatric social worker, he talked a great deal, and quite spontaneously, about his dislike of the school and his new teacher. No instance of a paraphasic use of words was noticed in the clinic at this stage, although instances, reported later, had already been noticed by the parents.

Constructional Ability. Three dimensional constructional ability has already been described. Formal tests for two dimensional constructional apraxia also were carried out accurately/

accurately enough but abnormally slowly. He was shown a square made with four matches and the examiner said "See that?". The patient replied - "A box. Three matches. A box". The four matches were then jumbled up. Without any instruction the patient began to reconstruct the square. He completed the two sides and the base correctly. The fourth match was lying well to the left of the figure (the side of his field defect). With his eyes on his design the patient fumbled with his right hand to the right of the figure. Suddenly he noticed the match on the left and then, abnormally slowly, and with a certain amount of difficulty, he completed the square reasonably well.

Counting and Calculation. At the same time an attempt was made to assess his ability to count and his powers of calculation. Four matches were put out lying in a row. The examiner said, "How many matches?". - to which the patient replied "Four". Six matches were then put out and the examiner repeated the question. The patient then said "Two ----- five", then, after much thought, "eight". He was also asked if he could do sums. Examiner: "What's two plus two?". Patient "No".

Identification of Fingers. An attempt was also made to get him to identify his fingers but his ability to do so was difficult or impossible to assess. It may have been unimpaired and his lack of response may have been merely the result of his auditory aphasia:-

- Q. "Show me your thumb" (This was repeated several times without any response).
- Q. "Which is your thumb?"
- A. (The patient looked perplexed and then opened his mouth very widely).

Q. "Which is my thumb?" (Examiner held out his own hand)

A. (The patient held up his own right hand).

Q. "Which is my thumb?"

A. (The patient held up his left hand)

Q. "Take hold of my thumb".

A. (The patient did so)

Q. "Show me your little finger"

A. (The patient hesitated)

Q. "Show me your pinky"

A. (The patient pointed to his left little finger).

Drawing and Copying. He could not be prevailed upon to draw a bicycle or a flower. He was shown a triangle, a circle and an inverted "T" and the printed word "cat" and with each he was given the instruction "copy that". The results are shown in Fig. 18a. He also, on request, drew a clock (Fig. 18a)

Although some of these findings were suggestive of parietal lobe dysfunction, many of the patient's abnormal responses may have been due purely to his auditory aphasia or to other causes.

Prehospital examination.

The patient, while attending the out-patient clinic, was, by 10th October 1953 not only unable to read but it had by then become impossible to get him to write at all ---- even single letters or figures. He was show^{ing} at times, curious involuntary and very slight rhythmic movements of the head and neck. He was also beginning to show other slight but more definite physical signs of organic nervous disease. Thus his legs had become rather stiff and there was an inconstant/

inconstant extensor plantar response on the left. Although macular vision was unimpaired he had a left homonymous hemianopia and Wernicke's hemianopic pupil reaction was demonstrable. It was on the basis of the history, of these clinical findings and of the opinion that the lesion must be too diffuse to be a tumour that a provisional diagnosis of Schilder's disease was then first made and because of this it was decided that the patient ought to be admitted to hospital for special investigation.

INVESTIGATIONS IN HOSPITAL.

By the kindness of Dr. Hutchison he was admitted to the Royal Hospital for Sick Children, Glasgow on the 20th October, 1953.

Physical Condition.

The general physical examination of the various bodily systems was normal. The Blood W.R. was negative

Central Nervous System - The optic discs appeared to be normal. The left homonymous hemianopia was still in doubt to some examiners but not to the author. Cranial nerves showed no abnormality. Tendon reflexes were present and symmetrical - the knee and ankle jerks being increased. Bilateral extensor plantar responses.

Lumbar puncture (21.10.53) gave 8 c.c. crystal clear fluid under normal pressure. Pandy test negative. One cell/c. Protein 35mgm. Sugar 70.5 mgm. Chloride 748 mgm. per cent. Lange 2221100000.

X-ray of the skull (23.10.53) suggested some cortical atrophy.

E.E.G. Report (26.10.53) stated that the patient was co-operative/

co-operative during the examination although his behaviour had not been quite normal. The record had shown a basic occipital rhythm that was markedly unusual, and which had consisted mainly of very slow waves with occasional frequencies as fast as 6 c/s. This slow wave activity had appeared to have had slightly greater amplitude on the left side. The record from the frontal area had been rather masked by muscle activity. The record taken from the right and left sides had shown that the slowest abnormalities appeared to be occipital. It had not been possible to get the boy to hyperventilate, and stroboscopic activation had not been used. In summary, the record had shown a gross slow wave abnormality which had appeared to be bilateral but more marked in the occipital region (Dr. J. R. Davidson).

Air Studies. (November, 1953) had shown a moderate generalised dilatation of the whole ventricular system with a fair amount of air over the hemispheres indicating a moderate degree of cerebral atrophy.

It was felt that all these findings supported the clinical diagnosis of Schilder's disease.

Mental Examination.

While in hospital psychiatric observation and study continued.

Vision - By the end of October, 1953 it was thought that in addition to the left homonymous hemianopia there was also some reduction in the peripheral part of the right upper quadrant of the visual fields. When looking through a picture book, however, the patient could still recognise objects without any difficulty whatever and in fact he described spontaneously to the doctor the various people and things depicted/

depicted in the book. For example, when looking at one series of pictures which was of clocks with faces drawn on them, he laughed and pointing to the various components said "Clocks, funny clocks - a boy - a face - he's opening the door - a motor's coming - the clock's swimming, all of which were correct observations. He described the various elements in another picture as follows:- "A boy and a lassie and a barrow and a doll and a book". That description also was quite accurate except that the "barrow" was in fact a tricycle and it is just possible that this was a first slight indication of a visual object agnosic difficulty. He described accurately and in some detail all the figures in a seaside scene and recognised without difficulty, various conventionalised outline drawings by the doctor, e.g. a matchstick man was described as "a funny man".

Alexia - Despite the fact that the child still had no visual agnosia he continued to have a verbal alexia which was complete. Thus when asked to read the title "Seaside Days" printed in large letters beneath one of the pictures he had described he said very carefully and deliberately, pointing at the letters with his finger as he did so, "Bay, By". Moreover, as he did so, he was pleased with himself and seemed to think he had read the words correctly.

He was then shown a series of capital letters individually, beginning with his initials and passing on first to letters of symmetrical form and then to those of unsymmetrical form. He responded as follows:

W ----- "half a.....(some unintelligible sounds).....William" (It was thought incidentally that the response here of "half a - " may have been due to a paraphasic association with the "double" of "double-u")

N ----- "don't know"
 T ----- correct
 A ----- correct
 X ----- "William Niam". (Sic)

All other letters, however, whether of symmetrical or non-symmetrical form, he did not recognise so that in addition to a complete verbal alexia he also had an almost complete literal alexia. He could not be induced to tell the time from the clock faces in the picture book, but this may have been due to the fact that he did not really understand requests for him to do so.

Hearing - His understanding of spoken speech was indeed more severely impaired as was apparent from further conversation with him. For example, when he was looking at the picture book with the doctor he had suddenly turned and said "Doctor, does the hospital lock up at Christmas time?". The doctor seizing upon the topic which was interesting the patient made several remarks containing the word "Christmas". The patient, however, (irrelevantly in fact to any of the doctor's questions) went on to say, "A big tent and a big Indian set -----I've got a pound". The doctor then said, "Are you getting an Indian set?" and the patient replied, once again irrelevantly "Yes, I've got two goldfishes and I had other fishes". The patient's very variable lack of understanding of spoken speech, without there being any actual deafness was shown strikingly by the following. It was known that he possessed, and was interested in, a pet rabbit and the doctor therefore decided to ask him about this using repeatedly various forms of sentence containing the word "rabbit". However, the patient's replies to these enquiries were all totally irrelevant and made no reference either to the word or to the idea of "rabbit". Finally, the doctor abandoning the/

the use of the spoken word "rabbit" drew a rough picture of a rabbit and showed it to the patient. With a laugh of delight he immediately exclaimed, "A rabbit - it's tail!" When he was then asked once more, and in a quiet conversation: al voice, if he had a rabbit he answered "Aye, a grey and white one".

Speech - His spontaneous speech was still only showing very occasional minor errors. Once when describing a picture of a little girl skipping he remarked "Lassie Skap". He had then paused, had thought for a second as if he realised he was not speaking correctly and then had said, correctly, "skipping".

TERMINAL OBSERVATIONS.

He was discharged from hospital on 21st November, 1953 but was visited in his home from time to time.

General - His emotional and intellectual state showed a marked, steady, deterioration from the end of 1953 (8 years 4 months). By then, he was, even during interviews, irritable and difficult. Later he became destructive of his clothing and laughed a great deal at night-time for no reason. It will be recalled that as a baby, he had been described as "a great laugher". His mother volunteered the observation that he now seemed to be insensitive to pain.

Vision - His visual fields were showing a very marked diminution by December, 1953, so that although he could still take hold of toys, look at them and smile about them, yet it was not clear whether when looking at them, he could recognise their nature and he certainly did not play in the normal manner with a bus and a toy monkey brought by the/

the doctor. He just held them and looked at them albeit in a pleased way. By February, 1954 he quite certainly did not recognise any visual objects and indeed did not by then seem to respond even to light.

Hearing.- His understanding of spoken speech had so deteriorated by Christmas 1953 that he was quite unable to understand anything the doctor said to him and by the early weeks of 1954 even his mother could not make him understand anything. Thereafter he gradually became quite deaf also.

Speech - His spontaneous speech was mumbled by December 1953. He did not speak much and if he did his speech was difficult to follow. After February 1954, even his mother could not understand anything he tried to say.

He was re-admitted to hospital on 10th April, 1954. By that time he was unable to stand, walk or feed himself. His emotional instability was then masked by a profound dementia. He was blind, deaf and incontinent of faeces and urine. His bodily attitude was characterised by general spasticity with the legs and feet extended and the head and neck slightly so, and the arms and wrists held flexed over the chest. Terminally, he developed a persistent unexplained high fever which did not respond to penicillin and he died eight days after admission at the age of eight years and eight months after an illness which had lasted for about 32 months.

AUTOPSY FINDINGS.

External Appearances.

The body was that of a well developed but rather poorly nourished boy of body length about 120 centimetres. There was/

was no external evidence of disease or injury.

General Bodily Systems.

Alimentary System. The peritoneal cavity was healthy. The oesophagus was unexceptional. The stomach mucosa showed a mild etat memelonno. The intestines showed no features of note except for the presence of rather scyballous masses in the colon. The liver (800 gm.) showed no gross change. The gall-bladder was healthy and the biliary passages were patent. The pancreas (40 gm.) was normal. The spleen (40 gm.) showed no marked change.

Genito-Urinary System. The kydneys (R.K. 57 gm. L.K. 53 gm.) were normal in all respects. The renal pelves, ureters and bladder were free of infection. The testes were present just proximal to the internal ring. The prostate showed no features of note.

Endocrine System. The adrenals (R4 gm. L.5) showed no abnormality nor did thyroid or pituitary. The thymus was involuted.

Cardio-vascular System. The pericardium showed an adhesion of firm nature between parietal and visceral layers of the right ventricle. The visceral pericardium was more opaque and thicker than usual. The heart (136 gm.) was rather long and narrow in shape but routine examination showed no abnormality of chambers, valves, great vessels or coronary arteries. The myocardium appeared to be of good quality.

Respiratory System. The pleural cavities were dry. The lungs (R.L. 300 gm. L.L. 250 gm.) were more voluminous and crepitant than normal. Congestion was not a feature. A few small areas of possible inflammation were noted on the left side. The trachea and major bronchi contained a little aspirated/

aspirated gastric content.

General histopathology. Heart - there was no abnormality of myocardium or coronary vessels. Thyroid - was unexceptional. Trachea - showed marked autolysis, but there was a suggestion of submucosal infiltrate still visible, There was thickening of the basement membrane. Lungs - there was patchy pulmonary oedema. Anthracosis was very slight. The larger bronchi were autolysed but basement membrane thickening was still evident. There was some emphysema. Interstitial eosinophils were noted, and there was mild patchy alveolar pneumonia. Liver - showed minimal fatty changes. Spleen - Lymphoid tissue was fairly prominent with central reactive change. There was some arterial hyalinisation. The pulp was cellular and contained numerous polymorph cells probably eosinophils. Haemosiderin was present in fair amount. Kidney - was a little congested but showed no striking change. Submandibular glands - showed patchy round cell aggregates. Pancreas - was unexceptional, as were the Adrenals and Pituitary. Stomach - showed autolysis. There was some round cell infiltrate but no gross congestion. Prostate - was healthy. Testes - showed rather excessive interstitial fibrous tissue. Germinal cords did not show good lumens and the cells were not arranged in orderly double layers.

Central Nervous System.

Gross Inspection. The cranial cavity and meninges showed no abnormality and the middle ears were free of infection. The brain weighed 1400 gm. and showed no obvious evidence of disease on inspection. The colour was normal and the consistence firm.

Primary Section. One primary section was made through the level of the basal ganglia, the section being at a slightly higher level in the left hemisphere than in the right. On inspection of the cut surface, the dilatation of the ventricles noted in the pneumoencephalogram was confirmed. The grey matter appeared to be normal and at first the white matter of the brain substance itself was also of normal appearance. However within about a minute of exposure of the cut surface to the air and to the fluorescent lighting of the post-mortem room definite changes in the appearance of the white matter became apparent. Anteriorly there was little alteration but posteriorly the white matter developed a greenish grey and almost fluorescent, appearance which, within the next few minutes, subsided, leaving a moist, greyish, translucent and rather gelatinous surface.

The affected areas of the white matter were more or less symmetrical but slightly more extensive in the right hemisphere than in the left. The gelatinous areas on both sides were continuous with each other through the splenium of the corpus callosum, which was itself affected. On the left, the lesion extended from the posterior part of the insula to the centre of the occipital white matter, the posterior boundary showing some increased vascularity and the white matter of the occipital pole remaining unaffected. Invasion of the subarcuate white matter was only to be seen in the anterior, parieto-occipital, part of the lesion. On the right, the lesion extended symmetrically but approached rather nearer to the occipital cortex. The posterior boundary of the lesion here showed a pinkish blush. Again, the subarcuate white matter was spared except anteriorly where invasion/

invasion had clearly taken place.

In the region of the basal ganglia, on both sides, there was some blurring of the markings.

Neurohistopathology.

Frontal Region of cerebrum showed slight perivascular oedema and some congestion of white matter.

Parietal cortex. There was some congestion and oedema and early demyelination with some swelling as seen in Loyez stain.

Region of insula. Apart from some perivascular cuffing of lymphocytes the grey matter was relatively unaffected. The white matter, however, showed very gross perivascular infiltrates with much vacuolation, swelling and hyalinisation of cells. Gemastete forms were seen. There was partial demyelination here without gliosis. There was moreover a transition to completely demyelinated areas, again without gliosis, and here the appearances were of a very open loose simple fibrillary network in which scanty spidery cells were seen.

Occipital cortex showed, anteriorly, rather similar changes but of milder degree. There was demyelination with swelling and fragmentation.

Basal ganglionic region. Here again the white matter showed perivascular cuffing, vacuolation of cells and formation of gitter and gemastete cells. Demyelination was observed, but there was no gliosis.

Optic nerves. These showed the central demyelination which had been visible macroscopically.

Region of pons - brain stem. The region of white matter just ventral to the nuclei showed vacuolation and the blood vessels/

vessels were surrounded by lymphocytes.

Medulla showed no very gross changes but posteriorly there was moderately obvious vacuolation of the white matter with occasional gemastete astrocytes present. There was no perivascular cuffing.

Cerebellum showed no obvious abnormality of grey or white matter.

Cerebral penduncle showed no obvious abnormality.

Upper cervical cord. There was perivascular cuffing of lymphocytes. The posterior horns were rather poorly defined and there was demyelination of the lateral descending columns without gliosis.

Lower cervical cord. There was only slight perivascular cuffing but demyelination of the lateral columns was noted again.

Upper and lower dorsal cord. The appearances were essentially similar to those seen in the lower cervical.

Lumbar cord. The appearances were again essentially similar.

Special Histological Enquiry

With the intention of studying directly the relative involvement of Flechsig's myelinogenetic zones, a series of 45 blocks of cortical tissue, with their underlying white matter, were removed. It was found, that the blocks did not in fact correspond accurately to the appropriate zones and that many probably included portions of other zones. However, the degree of involvement of the subarcuate white matter was studied comparatively in each block and the findings are shown in Fig. 21(a).

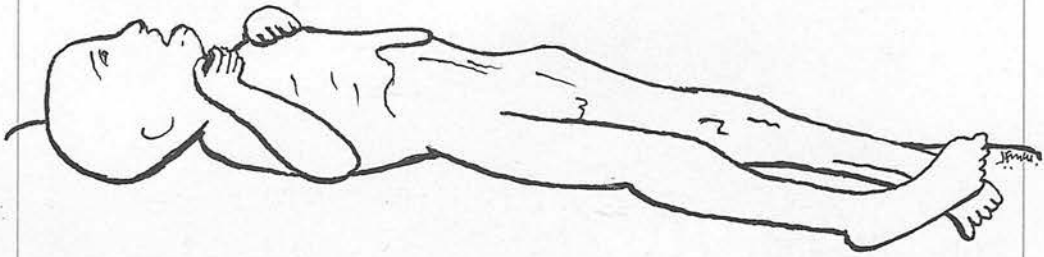


Fig. 19. The bodily attitude shortly before death.



Fig. 20. Primary section of the brain showing ventricular dilatation and marked demyelination in the white matter of the parieto occipital region. There is subarcuate sparing in most areas but invasion has occurred into the supramarginal gyrus and lower part of external capsule and insula, the internal capsule being spared, on both sides. Note the pinkish blush at the edge of the lesion on the right side. The condition is more advanced on the right than on the left.

Block Number	Degree of Subarcuate Involvement
1	o
2	o
3	o
4	o
5	+
6	+
7	o
8	o
9	+
10	o
11	o
12	o
13	+
14	o
15	o
16	+
17	o
18	o
19	+
20	+
21	++
22	o
23	+
24	+
25	o
26	o
27	++
28	+
29	o
30	o
31	++
32	o
33	o
34	o
35	o
36	o
37	o
38	+
39	o
40	o
41	++
42	++
43	o
44	+
45	o

Fig. 21(a) Table showing the degree of subarcuate involvement in 45 cortical blocks. The blocks were intended to correspond to Flechsig's 45 myelinogenetic zones but it was found that the degree of correspondence was probably very inaccurate.

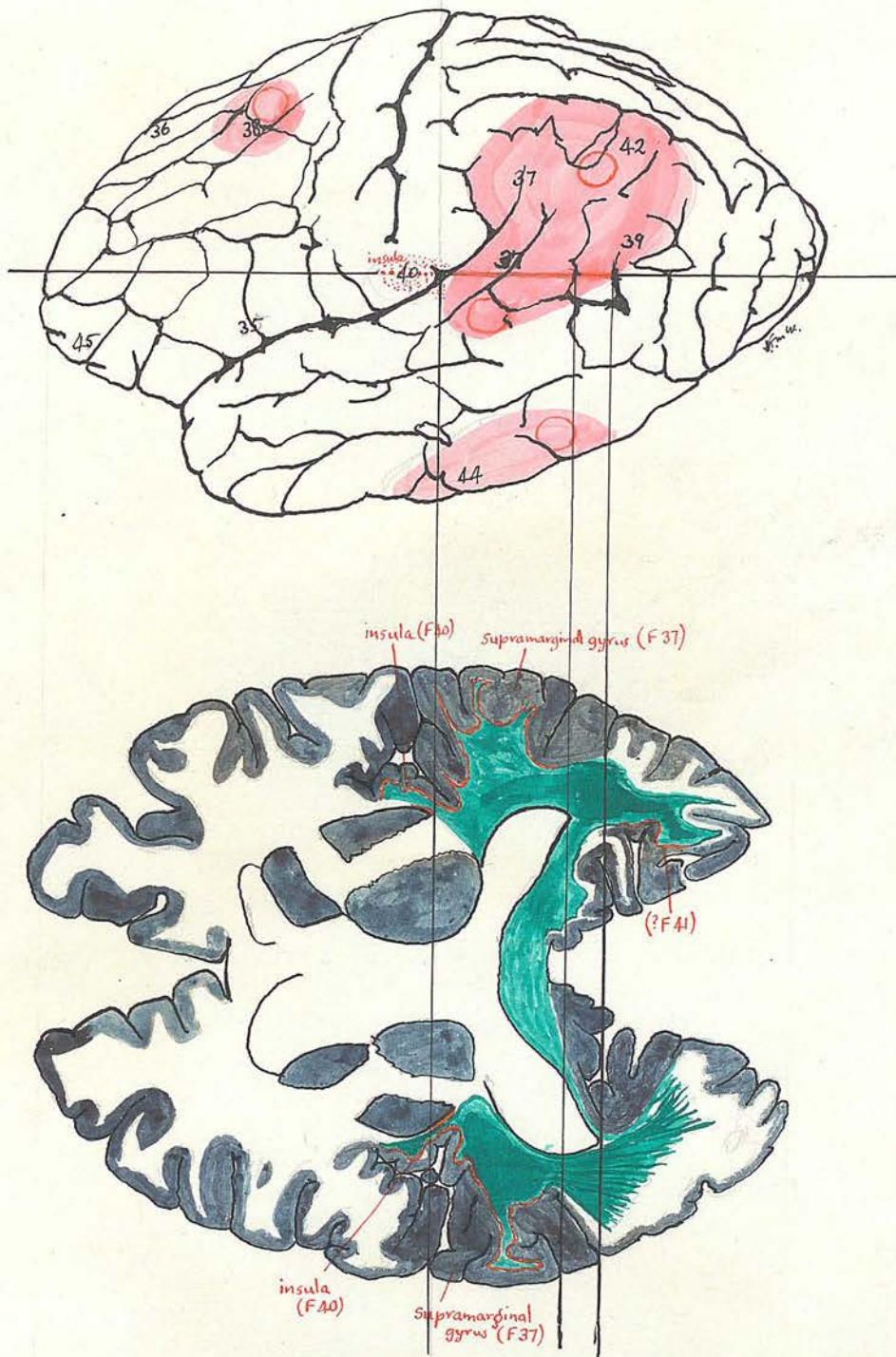


Fig. 21(b) Diagram of brain in Case 2, based on the findings in the primary section (Fig. 20), in the multiple blocks (Fig. 21(a)) and on general clinical considerations, to show suggested sites of subarcuate invasion in relation to Flechsig's terminal myelinogenetic zones.

- indicates site of subarcuate invasion seen in the primary section (Fig. 20)
- indicates approx. sites of blocks showing marked subarcuate invasion.
- indicates suggested regions of subarcuate invasion.
- Black numerals indicate Flechsig's terminal myelinogenetic zones.

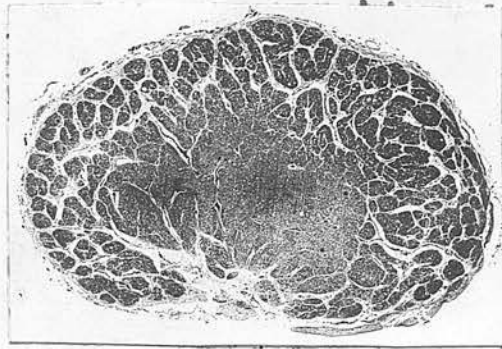


Fig.22. Optic nerve to show central demyelination. Loyez
Stain X 12.

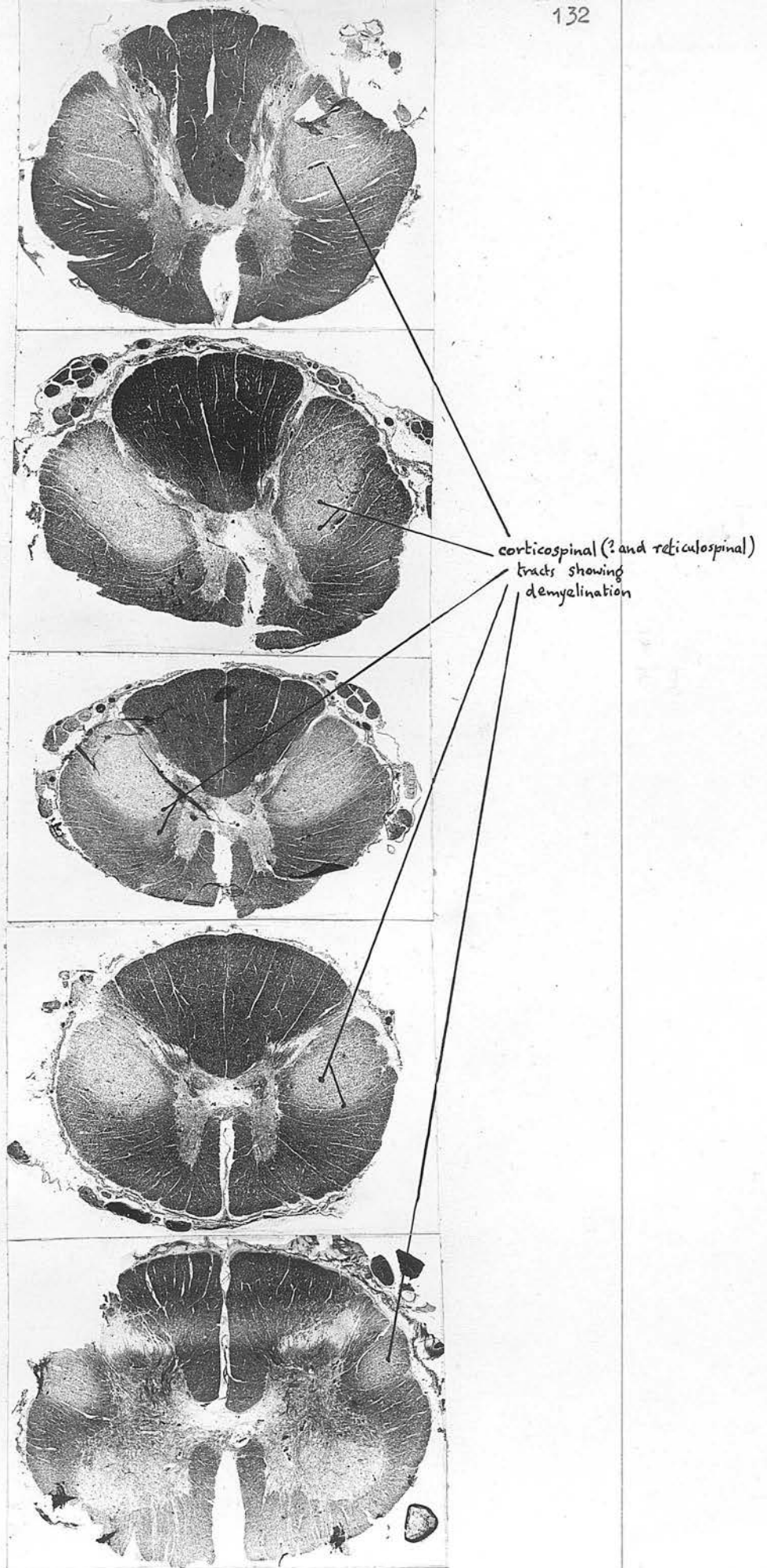


Fig. 23 Spinal cord, stained by Loyez method, to show demyelination of cortico-spinal and, possibly, reticulo-spinal, tracts in the lateral columns. Demyelination did not extend into the internal capsule.

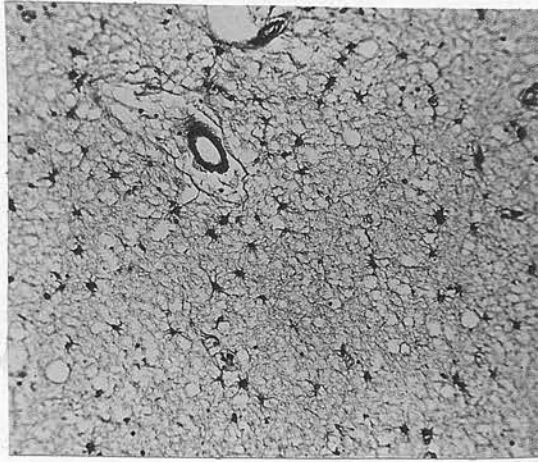


Fig.24. Low power view of demyelinated area of brain.
Haemalum and Eosin X 105.

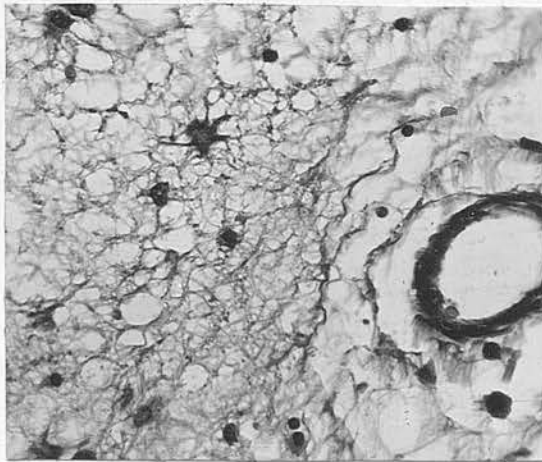


Fig.25. High power view of similar area. Haemalum and
Eosin X 300.



Fig.26 Area of white matter showing moderate demyelination. Loyez. Stain X 300.

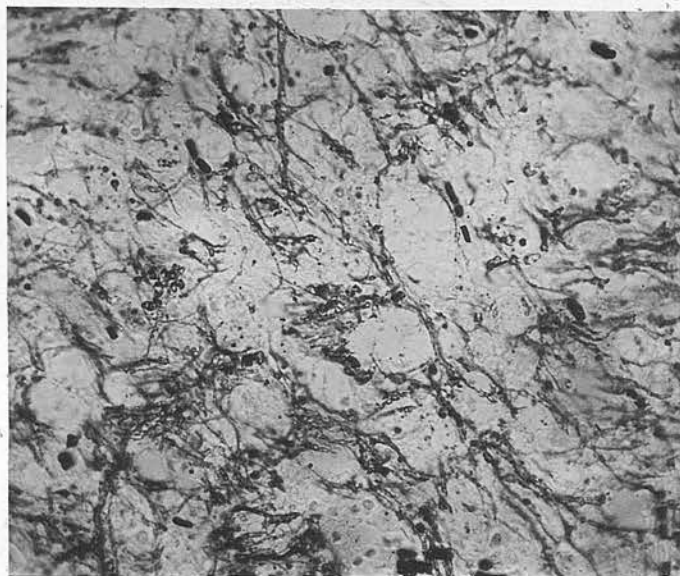


Fig.27. Area of less severe demyelination showing beading of remaining myelin sheaths. Loyez. Stain X 300.

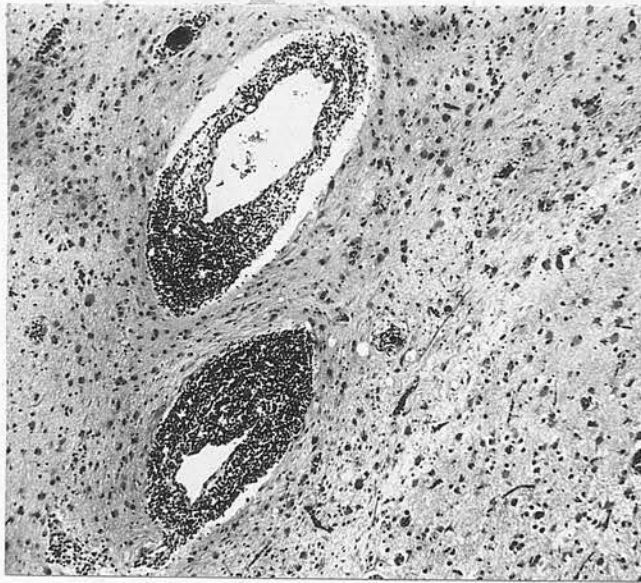


Fig. 28. Section from basal ganglion region to show more acute appearance of perivascular cuffing by round cells and increased cellularity of white matter. Haemalum and Eosin X 65.

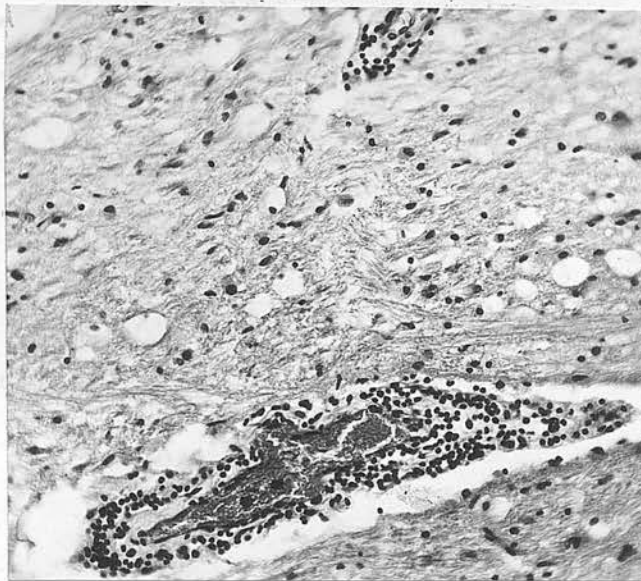


Fig.29. High power view of vessel ensheathed by round cells and occasional macrophages. Note vacuolation of associated white matter. Haemalum and Eosin X 105.

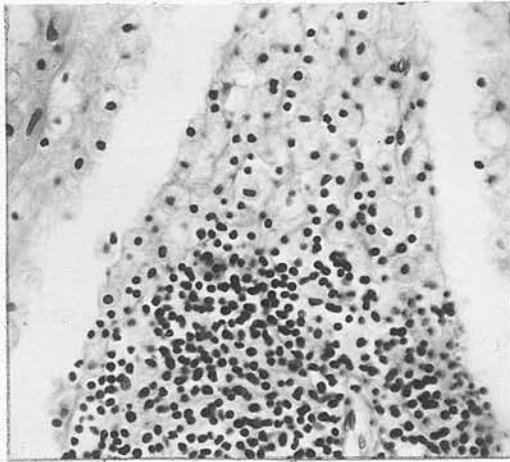


Fig.30 High power view of vessels showing obvious gitter cells accompanying lymphocytes. Haemalum and Eosin X 300.

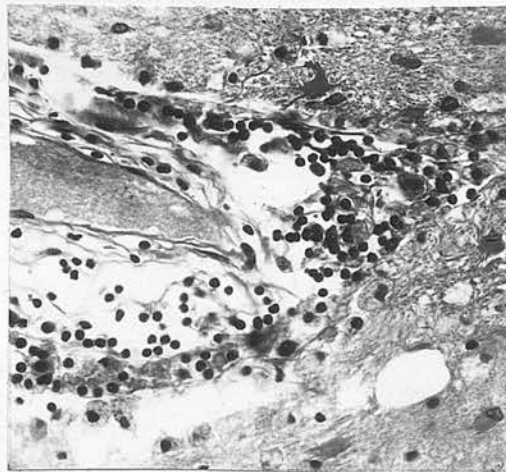


Fig.31. Similar view to show less marked infiltrate in more advanced area of change. Haemalum and Eosin. X 300.

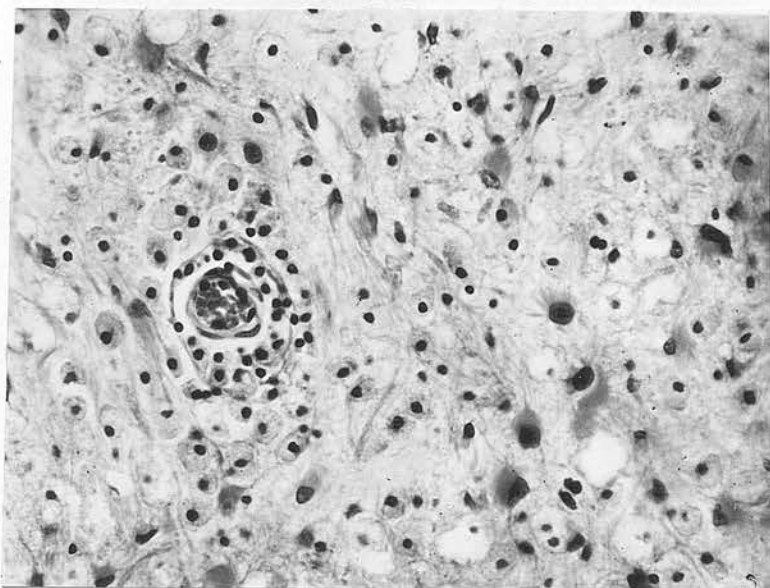


Fig.32 High power view of white matter to show very numerous foamy gitter cells and hyaline gemastete astrocytes. Haemalum and Eosin. X 300

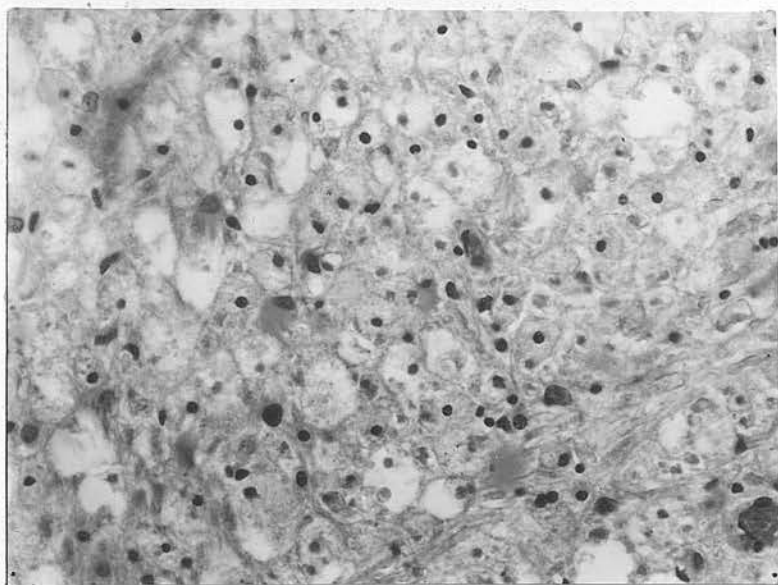


Fig.33 Similar view with very numerous gitter cells associated with severe demyelination. Haemalum and Eosin. X 300.

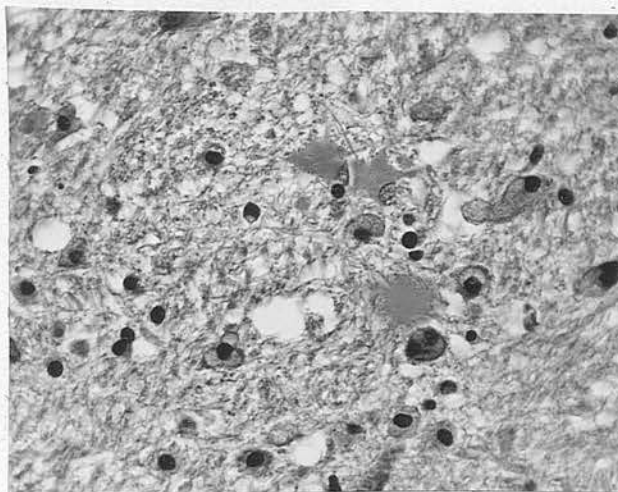


Fig. 34 High power view to show hyaline appearance of gemastete astrocytes.

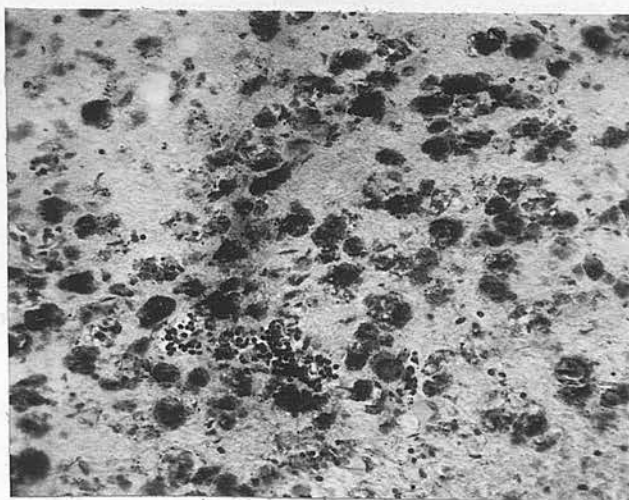


Fig. 35 Lower power view of area with many glitter cells containing myelin breakdown products which stain at this stage P.A.S. positive. Periodic-acid Schiff Stain X 150.

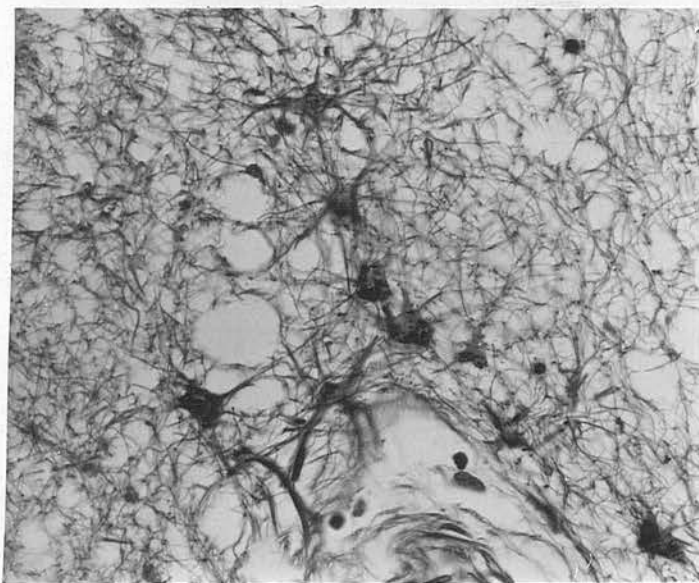


Fig. 36 Gliosis following demyelination showing spider astrocytes. Phospho-tungstic acid haematoxylin X 480.

CASE 3. AN ADOLESCENT.

ALEXANDER D. (died aged 19 years 11 months).

Presenting features - Personality deterioration.

ANAMNESIS.

The history was obtained from the parents, the patient, acquaintances and the school and army authorities.

Family History.

Father - aged 50, a woodcutting machinist, in good health. Paternal grandfather - died aged 79 of pneumonia and had previously been very healthy. Paternal grandmother - died when the father was aged two and the cause of death is therefore unknown.

Mother - aged 49, an intelligent healthy woman. Maternal grandfather - killed in an accident 26 years ago. Maternal grandmother - died suddenly of 'heart trouble' 23 years ago.

Siblings (1) Patient (aged 19), (2) Sister (aged 17), healthy, (3) Brother (aged 11), healthy doing well at school (4) Brother (aged 9), also doing well at school.

There was no history of mental illness in the family.

Personal History.

The patient was born on 15th January, 1933, the birth being prolonged but normal. He was breast fed for about a year, after which he was walking and talking and had bladder control. At school he was looked upon as a quiet, capable and willing boy. He was of average intelligence and quite a good scholar, passing his qualifying examination at the age of 12. During his last 2 years at school he was described as a likeable happy boy, interested in his school work/

work and anxious and eager to do it well. Although his teacher noticed no falling off in his work during these two years it was felt that he could have done better if he had chosen. The teacher saw him several times even after he left school and thought that he seemed to be happy and normal.

After leaving school at the age of 14 he worked in a bricklayers' yard for a few months and then as a grocery assistant with the Co-operative Society for a period of four years. He was considered to be a good worker and his job was to be kept open for him when he went into the Army at the age of 18 in May 1951. His insidious mental illness did not become obvious until he had been in the Army for about a year.

Previous Personality.

He was always a happy but rather solitary nature and in this respect was very different from his brothers and sister who were all extroverted.

Previous Health.

He had measles at the age of 3 months, and whooping cough later in childhood but no other serious illnesses.

Present Illness.

The onset was gradual over a period of several years.

The patient mentioned that between the ages of 12 and 15 he had occasionally had sudden faints in the mornings when going for the rolls or the papers, but there was nothing about his description of these faints to suggest epilepsy and after the age of 15 they did not recur except for a single 'blackout' in the Army at the age of 19 and for the terminal status epilepticus.

In his last 2 years at school (aged 13 to 14) he had seemed to become rather too content to drift and to be too open, friendly and unsuspecting but again these character changes were not looked upon as being grossly abnormal. On leaving school at 14 there was nothing to suggest any intellectual deterioration. However, when he went into the Army at the age of 18, he was placed in Selection Grade 4 so that some intellectual deterioration had probably taken place between the ages of 14 and 18 although it was apparently still not of such a degree as to be in any way noticeable to relatives friends or acquaintances. No details were obtainable about his general behaviour during his first year in the Army, but a report from his Commanding Officer during the latter part of his service said that he was able to complete a task 'only under constant supervision' and to absorb a fact 'only after explanation in great detail'. Apart from these reservations he had appeared to be 'average, mentally'. His personal habits were inclined to be dirty and he had been put on charges on three occasions for appearing on parade unshaven, for having a dirty towel, etc. and it is significant that his own family were indignant and incredulous on hearing of such charges.

In June 1952, at the age of 19 years 5 months, he was home on weekend leave and although no obvious abnormalities were observed he was noticed to be quieter than usual. Shortly after this, in the same month, he had a "blackout", he said, while cleaning rifles. There was no reference to this in his army medical documents although he had been admitted/

admitted to a medical reception station shortly afterwards because of "irrational behaviour" at his unit. On the night of his admission to the reception station he had been described as lost, confused, disorientated and unable to state any specific complaint. He ran around muttering that his mother was coming to see him and he seemed to be under the impression that he was in his home town, Glasgow. From the reception station he was transferred to Netley Military Hospital on 3rd July 1952, where he was found to be dull, simple, childish, vague and disorientated. It appears that his sense of time was disturbed for he said that he had been in the hospital for a year and a half. In hospital he wandered in and out of the ward office asking for his mother. There was no objective evidence of hallucinations and, moreover, he denied hearing voices. In appearance he was described as being "scruffy and untidy" but his physical state was satisfactory, in particular, there were no abnormal neurological signs. He was diagnosed as suffering from schizophrenia simple and was given E.C.T. without, however, showing any improvement. He appeared before a Medical Board and was discharged from the Army on 27th September, 1952 at the age of 19 years 8 months.

When he came home, he was restless and constantly walked about the room. He would, at times, sit and wring his hands, yet despite his anxious-seeming behaviour he was apathetic rather than anxious or depressed. He did not want to go out of the house or to think of taking up work. He had a strange expression on his face and seemed wandered or lost. Nevertheless he slept well and his/

his appetite was indeed larger than usual. At one time a visit from the Military Police, who had wrongly suspected him of being a deserter, upset him, but only slightly. Occasionally he gave a grimace or grinned and laughed to himself inappropriately. His personal habits deteriorated, he took little interest in his appearance and sometimes was incontinent of urine. He had a way of repeatedly turning his head suddenly to the side "as though he thought someone was coming up behind him" and this gave the further impression that he was frightened, suspicious and probably hallucinating. He never spoke about these glancing movements however, or offered any explanation for them and his conversation was not strange or indicative of hallucinosis.

INITIAL PSYCHIATRIC CONSULTATION.

He was first seen at the age of 19 years 9 months, at the Psychiatric Out-patient Clinic at the Western Infirmary, Glasgow on 3rd November 1952, having been referred there for an opinion by his own doctor. He attended with his mother who gave a description of his "lackadaisical" behaviour at home and gave information about the treatment he had had in the Army Hospital.

The patient himself did not formulate any complaints and denied having headaches. He smiled blandly during the interview and seemed to be remarkably indifferent about his condition and completely lacking in any insight. There did not seem to be any delusions, but occasionally, as already described, he glanced suddenly over his shoulder, as if distracted by an imaginary voice. On being questioned about this he denied hearing any such voice/

voice but the firm impression was that he was hallucinated. It was felt that he was suffering from schizophrenia of the simple-hebephrenic variety but he also gave the impression of being rather backward mentally and his mother's assurance that he had previously been "quite a clever boy" was accepted with reserve pending enquiry from other sources. The recommendation was made for the patient to be admitted to hospital for further investigation.

HOSPITAL INVESTIGATION AND TREATMENT.

He was admitted as a Voluntary Patient to the Glasgow Royal Mental Hospital on 8th November 1952 at the age of 19 years 9 months.

Mental Examination.

On admission he was co-operative but sat and grinned in a vacant way. His manner was rather simple. He was quite cheerful and although he expressed repeatedly a desire to go home he did not seem to be unduly worried about being kept in hospital. He was rather restless and shifted about in bed. His speech was free, but his voice rather thick and his enunciation poor. His attitude was one of nonchalance and he chuckled to himself from time to time during the interview.

The interview started with the patient saying "When will I get out? I would like to know when I am going out". He paused for a moment, pulled aside the curtain, looked out of the window and then went on, "Is that the drive? Not a bad place - birds! Is that the way out?". He heaved a deep sigh and continued "Och Aye. I am expecting my mother up this afternoon. Och Aye. That's life".

When/

When asked what he felt wrong he said he had had 'nerves'. He could not explain clearly what he meant by this but spontaneously gave examples of thought block and ambivalence as follows:- "Well, you would think of something and it would vanish all of a sudden. You might say 'I want to go to the pictures' and the next minute you would say 'No, I won't go to the pictures'". He was satisfactorily orientated as regards, time place and person and on the Kent Oral Test his mental age was assessed as 9.

Physical Examination.

The patient was a well nourished young man of good colour with a tendency to the deposition of subcutaneous fat. The tongue was moist and clean. He had his own teeth and they were in fairly good condition. He was co-operative in the physical examination. Cardiovascular system - pulse regular and of good quality, vessel wall not palpable, apex beat in 5th left interspace within the mid-clavicular line, no increase of area of cardiac dullness. The heart sounds were regular and of good quality. No murmurs. Blood pressure 132/86. Respiratory System - There was free movement, percussion note resonant, breath sounds, bronchovesicular, vocal fremitus and resonance equal and normal. Alimentary System - no abnormality detected. Central Nervous System - pupils equal central and circular and react to light directly and consensually and to accommodation. Fundi difficult to visualise but no abnormality detected. Tendon jerks easily elicited but not exaggerated. Abdominal reflexes present. Plantar responses both flexor. Blood W.R. negative. Haemoglobin (Talquist) 90%

Insulin Coma Therapy.

After a short period of observation a firm diagnosis of schizophrenia simplex was made and a course of insulin coma therapy was instituted on 24th November 1952. It is noteworthy that he did not experience any comas until the dosage of insulin reached 480 units. He had 20 comas without ill effect but, also, without improvement. Treatment ceased on 12th February 1953 (aged 20 years 1 month).

Progress.

Following insulin coma treatment he was, in his manner, forward and over-familiar and would not hesitate to interrupt a conversation. He was also apt to wet and to soil himself at times. His habits were very dirty and he would blow his nose on the bed clothes. At times he seemed almost stuporose and fatuous in his manner. He had put on a great deal of weight.

During the next three months he seemed to deteriorate gradually. At times he was rather restless and had to be put to bed. He would often appear about the ward naked but was weak and unsteady on his legs. He took his food well but had to be spoon fed. When in bed he took to sucking the bed clothes and when up he walked about on tiptoe. There were no abnormal neurological signs, however, and the plantar reflexes remained flexor.

TERMINAL OBSERVATIONS.

Six months later, aged 20 years 10 months, there was gross affective blunting and the general deterioration was more marked. It was scarcely possible even to engage his attention. He was unsteady on his feet and would collapse if not supported but there was still no spasticity in the legs/

legs although the plantar responses were equivocal. There was a suggestion of a sucking reflex and he would spend hours sucking the bed clothes. There was also a bilateral grasp reflex with forced groping. Glancing movements from left to right were now very frequent - at times continuous - and the fundi therefore were not seen. On 28th November 1953, for the first time, there was a definite Babinski sign on the right, with fanning of the toes, and usually, but not always, an up-going big toe on the left. The grasp reflex and forced groping were still present and so was the sucking reflex.

An E.E.G. report dated 4th December 1953 stated:-

"A great deal of delta activity from the posterior parts of the brain. There is no distinct focus".

He was seen by a neurosurgeon on 13th December 1953 but no further light could be thrown on the diagnosis. On 18th December 1953 he suddenly and unexpectedly went into status epilepticus at 8.15 and died at 11.15 a.m.

AUTOPSY FINDINGS.

External Appearances. The body was that of a young man.

There were no external signs of disease.

Thorax. The pleurae were normal. There was no excess fluid in either pleural cavity. The trachea and the large and small bronchi contained mucopus. There was a moderate degree of emphysema of the anterior parts of both lungs. Both lower lobes were firmer than normal. On section the marbled appearance and staphyloid arrangement of bronchopneumonic consolidation was seen. The pneumonia was firmly established on both sides and occasional areas of confluent consolidation were seen. The pericardium/

pericardium was normal. The heart was small. The myocardium, endocardium and valve cusps presented nothing of note.

The coronary arteries were not diseased.

Abdomen. The peritoneum was normal. The oesophagus,

stomach, duodenum, small bowel, colon and rectum showed no abnormality. There was no disease of the liver or gall bladder. The spleen was small and soft. The adrenals and pancreas showed no naked eye abnormalities. The kidneys were normal in size. The capsules stripped easily and there was no scarring. Sections revealed nothing of note. The renal pelves, ureters, bladder and prostate were not diseased.

General histopathology. Histological examination confirmed the presence of a well established acute bronchitis and bronchopneumonia. In the pituitary, a small foetal adenoma was present.

Central Nervous System.

Gross Inspection. The brain was small and there was an increase in the amount of cerebrospinal fluid in the subarachnoid space. There was no flattening of the convolutions, cerebellar coning or other evidence of a space occupying lesion. On the postero-lateral aspect of the parietal lobe, 4 c.m. from the median fissure, a small depression was present on each side. The brain was fixed prior to further dissection. Dissection revealed no naked eye abnormalities other than the depressions on the parietal lobes previously noted.

Histopathology. Representative histological sections of the cerebral hemispheres, cerebellum and brain stem on/

on first examination were at first said to reveal no significant features in the grey or white matter but re-examination of the sections a year later revealed definite abnormalities as follows:-

Region of Rolandic Fissure. There was congestion of miningeal and cortical vessels. The white matter showed marked perivascular cuffing by gitter cells and occasional gitter cells were present in the substance. Very occasional gemastete astrocytes were seen. The axons appeared intact: there was no demyelination or gliosis.

Frontal Lobe. There was slight congestion of cortex. The white matter showed rather cellular round-cell foci. Gemastete astrocytes were frequent while gitter cells were also seen. There was mild round-cell and gitter cell perivascular cuffing. The axons appeared normal but there was early swelling of myelin sheaths centrally in white matter. Fibrillary astrocytes were seen but there was no gross gliosis.

Hippocampal Region. The cortex was unexceptional. Oligodendroglia in white matter was rather prominent and in the substance occasional gemastete and gitter cells were present. In the perivascular spaces were round-cells and gitter cells in moderate number. Vacuolation of the substance was noted. Axons appeared normal but there was variable swelling of myelin sheaths where gitter cell cuffing was noted. There was perhaps slight gliosis.

Occipital lobe near calcarine fissure. The cortex appeared normal. There was some vacuolation of the white matter. In the perivascular spaces were small round-cell and gitter cell aggregates. Very occasional gemastete cells were seen./

seen. Axons appeared normal and there was only very slight swelling of myelin sheaths with no gliosis.

Hypothalamic Region. The mammillary body was congested. In the nearby white matter gemastete cells were present and perivascular gitter cells were present. There was vacuolation of the substance. Axon cylinders appeared normal but there was swelling of myelin sheaths and patchy demyelination with mild gliosis.

Region of Basal Ganglia. The white matter showed dilatation of perivascular spaces, sometimes with very marked round-cell cuffing, sometimes with gitter cells and sometimes with these mixed. Gemastete astrocytes were very numerous. The interfascicular oligodendroglia was prominent. In the internal capsule there was marked loss of architecture with suggestion of new vessel formation, and here demyelination was gross. Where cortex was present at one edge the arcuate zone showed retained myelin. Where demyelination was marked there was swelling of the sheaths with beading in longitudinal forms. Where demyelination was marked there was fragmentation of axon cylinders. In these areas fibrillary astrocytes were present and glia was being produced. Some astrocytes had thick unipolar processes.

Sudan black showed staining of perivascular gitter cells where the disease was moderately advanced. Mucicarmin staining showed staining of gitter cells around vessels especially where the disease was advanced. The material stained was rather lumpy sometimes while in the large gitter cells an impression of vacuolation was obtained. Free gitter cells in the cerebral substance were also sometimes stained.

Periodic acid Schiff stained also the perivascular gitter cells/

cells in the advanced lesion, in bright fashion. Free gitter cells were rather faintly stained. The perivascular cells stained were sometimes coarsely clumped, and sometimes finely granular or spicular. In some areas empty spaces in the substances showed a metachromatic effect outlining them.

Medulla oblongata. The grey matter was unexceptional. The white matter ventrally showed quite marked perivascular gitter cells and occasional gemastete forms. Here, there was myelin sheath swelling without gliosis while the axons appeared normal. Also in the cranial nerve roots there was a suggestion of beading of myelin sheaths.

Cerebellum. Appeared entirely normal.

Parietal Lobe. The grey matter was rather exaggerated with a suggestion of cortical infalling. In the white matter there was perivascular cuffing by round-cells while in others gitter cells were numerous. Lying free were gitter cell aggregates while gemastete astrocytes were numerous. There was demyelination centrally with swelling of myelin sheaths. The arcuate region was spared. Some fibrillary astrocytes were present but gliosis was not great. The axons were unexceptional.

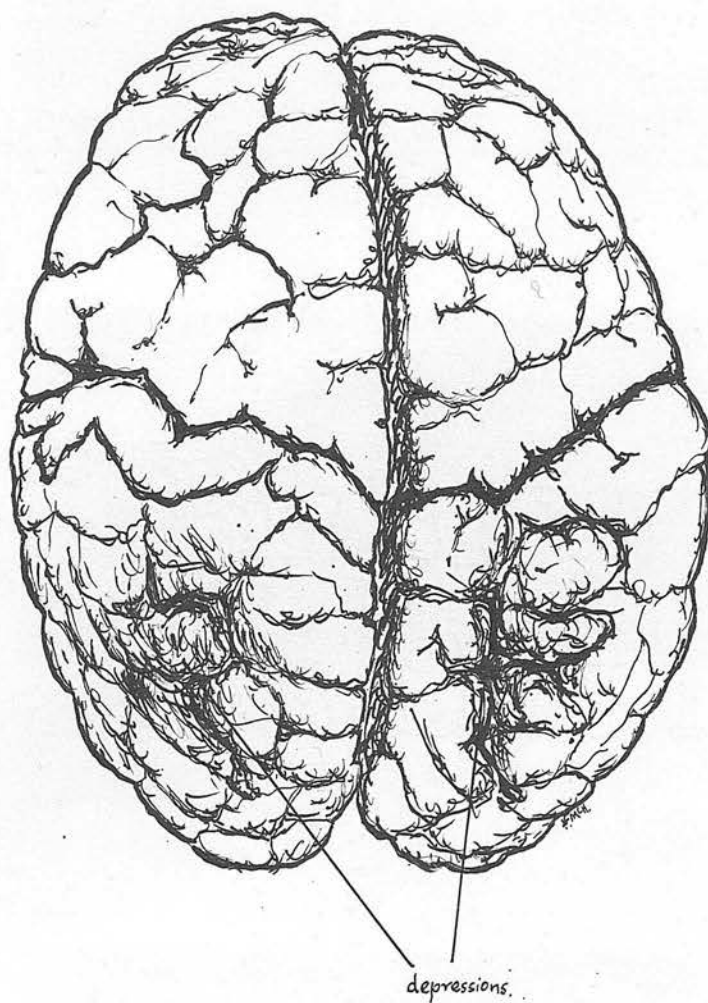


Fig. 37 Diagram to show the site of the two depressions in the parieto-occipital region of the brain in Case 3.

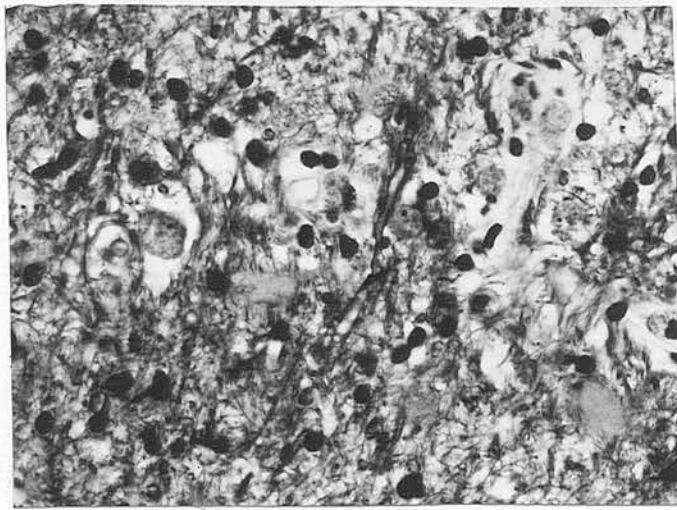


Fig. 38 Section from parietal lobe to show early changes in myelin sheaths. Loyez X 480.

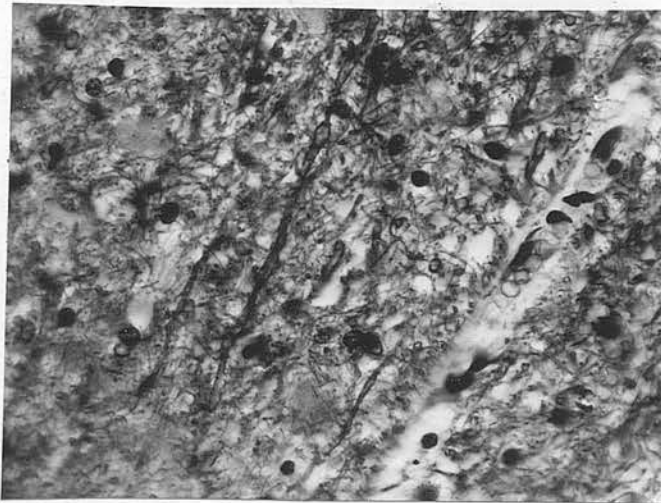


Fig. 39 Another view to show beading of myelin sheaths traversing photograph approximately vertically. Loyez X 480

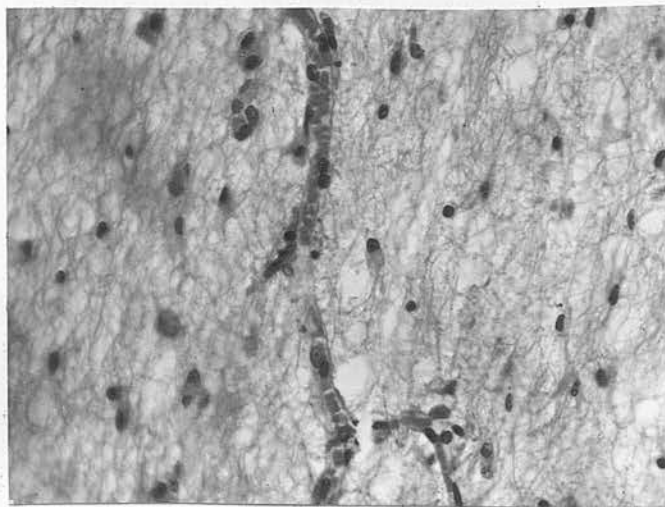


Fig.40 High power view of another part of internal capsule to show demyelination with some vacuolation. H.E.X. 300.

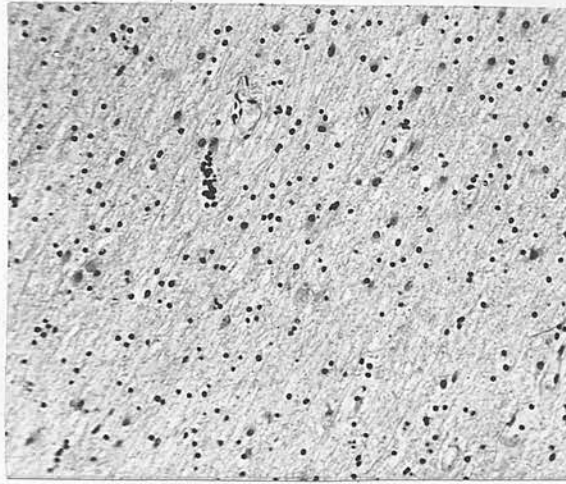


Fig.41 Low power view of frontal region to show increased cellularity of white matter and a focus of lymphocytes centrally. H.E. X 150.

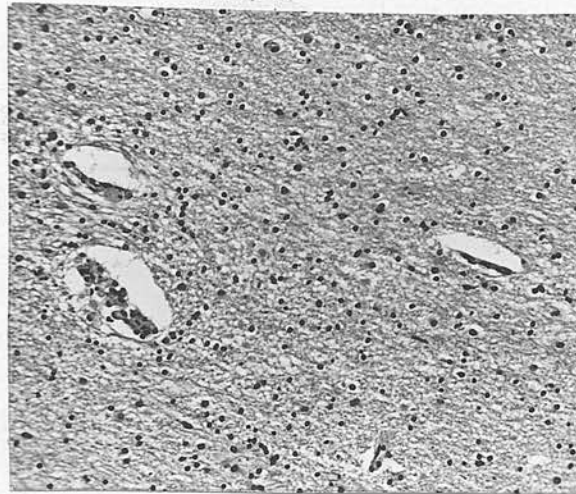


Fig.42 Low power view of parietal region to show slight increase in cellularity in this region. H.E. X 150

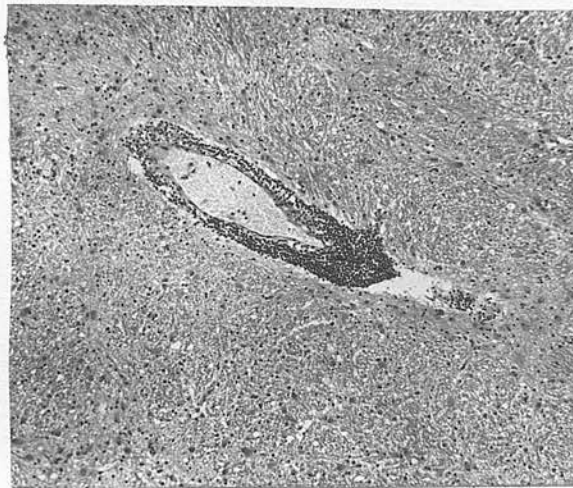


Fig.43 Low power view of internal capsule to show marked perivascular cuffing by round cells and increased cellularity of white matter. H.E. X 65.

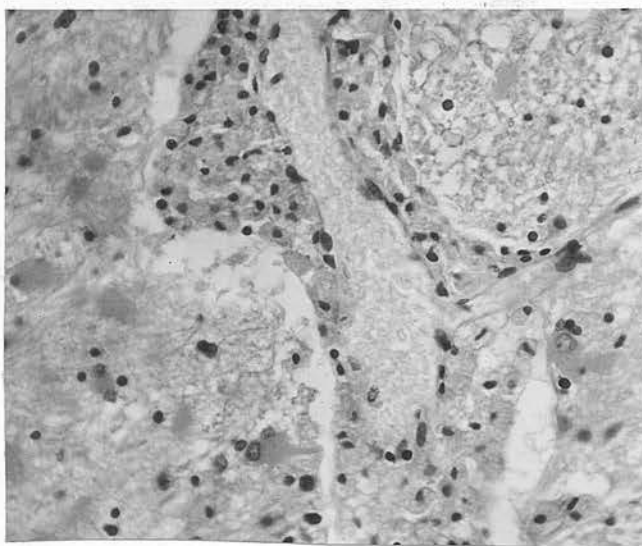


Fig.44 Another area to show vessel largely surrounded by gitter cells and occasional lymphocytes. Gemastete astrocytes are seen in the surrounding white matter. H.E. X 300

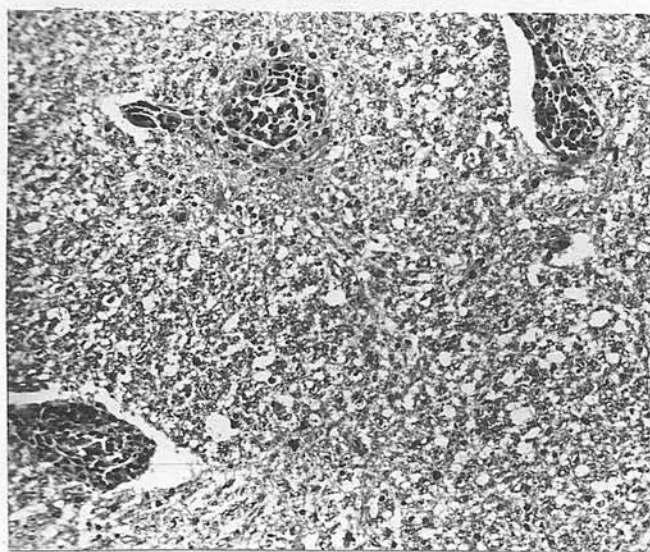


Fig.45 Medulla oblongata to show marked perivascular infiltration by round cells and gitter cells. Note also vacuolation of white matter. H.E. X 150.

4. DISCUSSION.

HISTORICAL ASPECTS.

The emphasis of interest in diffuse sclerosis has, from the late nineteenth century up to the present time, shifted from one aspect to another and each new approach to the disease has shed further light upon the problem. It has only been comparatively recently, however, that serious attention has begun to turn to the developmental aspect.

Originally, the emphasis of interest was mainly descriptive, many cases recorded by the early writers having been diagnosed only in the postmortem room - and then, as Balo (1928) pointed out, by tactile and visual inspection alone. According to Walter (1918) the first author to describe the clinical picture of the disease as it occurred in childhood was Heubner (1897) whose autopsy report on a boy of 5 was also confined to the gross tactile and macroscopical findings. Later, descriptive interest in the histological aspect was greatly stimulated by Schilder (1912) when he reported a distinctive case of his own in which, for the first time, it had been possible to carry out accurate histological examinations by means of newly developed techniques. In his original case report Schilder discussed the knowledge of the condition available at the time and described, also, four similar cases from the literature. In the following year Schilder (1913) described the pathology of one of these four cases, a familial case previously reported by Habermeld and Spieler (1912), in which he found a dense accumulation of 'prelipoid' substance and at the same time he added yet another case from the literature. Schilder/

Schilder, believing the condition he had described to be due to an inflammatory response to a toxic agent, called it 'encephalitis periaxialis diffusa'.

It was largely as a result of Schilder's early studies that the distinctive type of diffuse demyelination and sclerosis which he had described and which has since taken his name was better understood, that further work on the subject was stimulated and that various articles on it were published, especially in the continental literature. For some time, the main interest was in the inflammatory aspect and in the nature of supposed toxic or infective agents but, simultaneously, there were further advances in the purely descriptive and clinical fields. Collier and Greenfield (1924) stressed the importance of recognising the characteristic clinical picture of Schilder's disease and the possibility of diagnosing it during life and, in the same year, Bouman (1924) also published an important contribution to the subject. Both of these outstanding papers adhered to Schilder's term, 'encephalitis periaxialis diffusa' while, in a third paper of the same year Schilder (1924) himself reported yet another case, occurring in maturity, but differing markedly from each of the two previous cases he had reported. This was a case which subsequently seemed, to Lumsden (1951), to resemble the subacute sclerosing leucoencephalitis of van Bogaert (1945), a condition now considered to be infective and, by some, to be identical with the 'inclusion encephalitis' of Dawson (Brain & Strauss, 1957). Bielschowsky (1927), who had described a case characterised by fluctuations in temperature, had also considered infection to be of fundamental importance./

importance. Other reports appeared in which attempts were made to evaluate, also, degenerative and metabolic aspects (Globus & Strauss, 1928). Furthermore, the possibility of involvement of white matter elsewhere than in the cerebral hemispheres was pointed out by several authors in particular by Stewart, Greenfield and Blandy (1927) who drew attention to yet another feature, namely, the rapid course in some cases. Gasul (1930) reviewed the literature, recorded a case and tabulated 71 previously reported cases. Bouman (1934), in a second publication of outstanding importance and containing a very extensive bibliography, surveyed the whole problem of diffuse sclerosis and urged, in particular, the necessity for more diagnoses being made during life and for more accurate post mortem examinations being carried out.

Following the publication of Schilder's original papers several authors began to draw attention to a clear familial incidence in some cases and to attempt to distinguish familial from exogenous forms. Their observations led eventually to more detailed and systematic genetic studies by later workers. Moreover it was to some extent the increasing recognition of a very clear genetic causation in some cases which led to a growing appreciation of the importance, more generally, of inherent constitutional tissue factors. Einarson & Neel (1938, 1940, 1942), Einarson, Neel & Stromgren (1944), and Einarson (1951) in a series of case reports and comprehensive discussions on the problem of diffuse sclerosis distinguished various 'tissue factors' which they considered to be of importance. Norman (1947) also/

also discussed the tissue reactions in 'Schilder's disease' and reported the case of a patient who died, from the diffuse progressive metachromatic leucoencephalopathic form, at the age of 18 and in whom the metachromasia involved not only glial cells but nerve cells and cells of the gall bladder and kidneys. Norman on the one hand recalled that Nissl (1910) had been the first to make reference to the rare finding of metachromasia of both glial and nerve cells in diffuse sclerosis, an association which suggested a link with amaurotic idiocy and, on the other hand, quoted Witte's (1921) case as the only other reported example of Schilder's disease in which combined cerebral and visceral involvement had been demonstrated. He suggested that there was a relationship in such cases to the lipoidoses. Einarson (1951) reported a case, which he had demonstrated clinically, in which amaurotic idiocy and diffuse sclerosis were said to have been present in combination. Leslie (1952), who reported a second British case of the diffuse progressive metachromatic leucoencephalopathic form of 'Schilder's disease', did not think there was sufficient evidence for regarding the condition as a variety of lipoidosis.

Interest in the importance of the developmental background and in the possible influence of concurrently active histogenetic processes upon the tissue reactions in diffuse sclerosis has already been evinced by various authors. Thus, Globus and Strauss (1928) characterised the disease as an arrest, with subsequent dissolution, of the normal differentiation of brain tissues. R.M. Stewart (1956), who reported the case of a patient who survived for thirty/

thirty six years, thought that the smallness of his patient's brain was attributable not to the intensity of the sclerosis but to a developmental arrest occurring at the end of the first year of life and attributable, perhaps, to a dietary deficiency at that time. Greenfield (1933) and Brain and Greenfield (1950) attributed the late infantile metachromatic leucoencephalopathic form of the disease explicitly to a 'developmental' disorder of the lipid metabolism of the tissues of the central nervous system. Blackwood and Cumings (1954) devoted detailed attention to the histo-chemical aspects of the developmental background in a study of the brains of three cases -- all, however, occurring in the infantile period. Poser (1957), quoting the work of Kufs (1931), suggested that the brain of the child was less resistant than that of the adult because it had not yet had time to recover completely from some of the subclinical injuries of the benign exanthems and other infections. Poser stressed, furthermore, that diffuse sclerosis was not uncommon at a later period than childhood and that it occurred even in adult life. He also mentioned that it was now well established, in some cases, that the nerve tracts most severely involved were those myelinated last. Previously, Barré, Morin, Draganesco and Reys (1926) had found that diffuse sclerosis was an affection occurring at every age "from the first to the fiftieth year" having its greatest frequency "about the age of 20" while Brock (Wilson, 1940) commenting on the age incidence in a series of 33 cases, had said that there was an almost equal division between those under, and those over, 20. Lumsden (1957), who felt that the answer to the riddle of the demyelinating diseases would, be/

be delayed mainly because we did not yet know enough about the biology of myelin, emphasised the importance in this respect of the recent chemical evidence for the slow maturation between childhood and adult life, of the cerebral white matter and for a slow but constant metabolic turnover of myelin even in adult life.

Summary.

Since the end of the nineteenth century, the emphasis of interest in diffuse sclerosis of the brain has shifted from one aspect to another. After a predominantly descriptive period, interest turned successively to the inflammatory, degenerative and metabolic aspects, to the striking familial and genetic background in some cases and, more recently, to the various inherent tissue factors. Some of the observations recorded in the literature had indicated that the disease had its greatest incidence in late adolescence, suggesting that some terminal phase of myelin maturation might then be at its most active, and most vulnerable, stage. However, only with increasing realisation of the persistence up to adult life of active developmental changes in the white matter of the brain can it be expected that interest will turn more explicitly to the pathogenetic role, not only in diffuse sclerosis but also in the demyelinating diseases generally, of this late developmental activity.

CLINICAL ASPECTS.

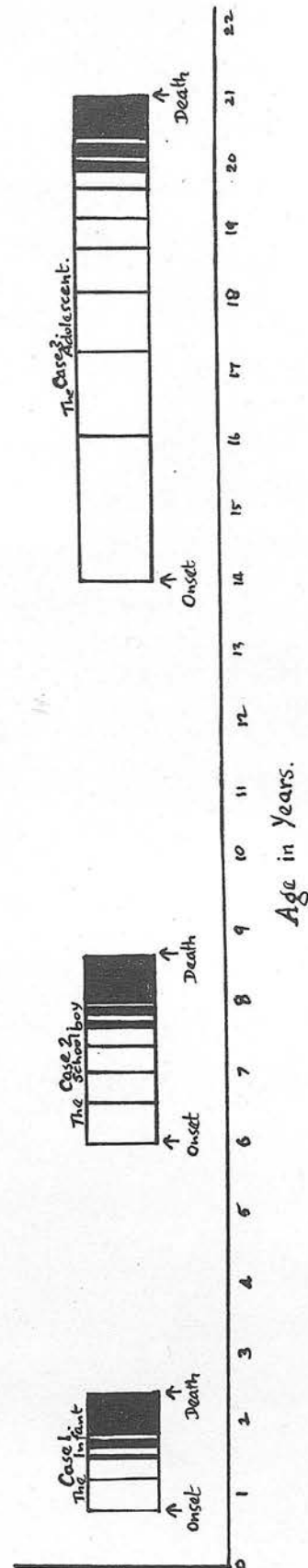
The onset of diffuse sclerosis, as 'Schilder's disease' is said to be acute, chronic or subacute. It has been described as 'abrupt' by Berliner (1955), and as 'within a few days' by Collier and Greenfield (1924) and the subsequent course to a fatal termination in such cases has been said to be rapid. Comparably acute episodes, with periods of temporary or partial arrest of the disease process, reminiscent of the spontaneous remissions more characteristic of multiple sclerosis, occur also in the chronic cases. Now, the influence of concurrent developmental processes upon the onset and course in acute and chronic forms of the disease may well be obscured, either by the suddenness or by the irregularity of the reaction, and it would be early and accurate observation of the initial symptoms, pre-eminently in the subacute forms, which would be most likely to be helpful in a developmental study. Wilson (1950) and others have recognised the distinctive nature of such subacute forms, in which the onset is insidious and the course slowly but steadily progressive.

Early symptoms of the disease are typically protean, presumably because of the variable site of the initial lesion but they seem to have, nevertheless, a degree of specificity for any particular age group. Thus, in infantile cases, motility disturbances are normally the first signs, with dementia occurring only late. Mental symptoms may occur as the initial features in juvenile patients, when they may take the form of agnostic or aphasic difficulties but such symptoms/

symptoms have hitherto received little attention, the chief early manifestation in such cases usually being said to be cerebral blindness (Collier and Greenfield, 1924). Early mental symptoms seem to be progressively more prominent in the older age groups. Pathological laughter has often been reported and Stewart, Greenfield and Blandy (1927) were interested in the fact that 'mania' had been reported by Flatau (1925) and by Brock, Carroll and Stevenson (1926). A greater number of patients seem to have shown mental symptoms of a schizophreniform nature - for example Roizin, Moriarty and Weil (1945) reported a 'schizophrenic reaction syndrome of catatonic type' in a 34 year old woman, Frowein & Krucke (1951) described a 'schizophreniform illness' characterised by affective and katatonic features and Bruetsch (1952) said that autopsy sometimes revealed severe cerebral disease, such as diffuse and extensive demyelination of the Schilder type, in what had appeared to be classical cases of schizophrenia in which no organic disorders had been suspected during life. By contrast with the earliest symptoms, the intermediate and late symptoms exemplify, irrespective of the age of onset, convergence towards a rather stereotyped state of dementia and decerebrate rigidity which is characteristic of the terminal stage of the disease.

Largely because of the variability of the clinical picture diagnosis is by no means always easy and, according to Collier and Greenfield (1924), 'Schilder's disease' was first recognised during life, by Collier, only /

Fig. 46. Duration of Illness in Relation to Age.



only after some twenty cases had been reported in the literature, Recognition of the disease at an early stage is particularly difficult because of the protean nature of the early symptoms and this is one reason why early mental symptoms are not usually studied in detail and, indeed, often escape notice altogether. However, the clinical study of diffuse sclerosis from the developmental aspect must depend very largely upon adequate assessment of the earliest symptoms against the concurrent behavioural and psychological development of the affected individual so that it is precisely early mental symptoms which, if studied satisfactorily, would throw the most light upon the influence of developmental factors, despite the fact that several authors have complained that early mental symptoms may impede the co-operation of the patient and make accurate examination difficult.

Now, all three of the cases reported here were of the subacute type and ⁱⁿ two of them, viz. the infant and the schoolboy, the correct diagnosis was made, clinically, at an unusually early age, ~~while~~ Even in the adolescent the diagnosis was strongly suspected during life. The initial symptoms, which were studied in detail, were variable but each case ran a subsequent course to a state of terminal dementia and decerebrate rigidity which was strikingly stereotyped. It was also noticed that the length of the illness was roughly proportional to the age of the patient (see Fig. 46)

Case 1. The Infant.

In the case of the infant, the onset at the age of 9 months/

9 months was insidious and the subsequent course slowly progressive to a fatal termination after a period of 20 months. The special senses were unaffected and the most striking early clinical features were motility deterioration, and loss of speech. Decerebrate rigidity only developed at a later stage and dementia was terminal. The comparative chronology of these symptoms is shown diagrammatically in Fig. 50.

The clinical diagnosis of 'Schilder's disease' had already been made, in this case, by Dr. A. W. Abramson, and confirmed by Dr. J. B. Gaylor, by the time of the first psychiatric examination, but it was then felt that the case resembled sufficiently closely the group of cases described by Greenfield (1933) and Brain and Greenfield (1950), under the name of 'late infantile metachromatic leucoencephalopathy', to justify making this more precise diagnosis. It was thought, indeed, that this was perhaps the first occasion on which this diagnosis had been made on purely clinical grounds for Leslie (1952), who had reported the pathological findings in such a case, said that this precise form of the disease had never been recognised as such during life. However, Jefferson (1958), who also mentioned that in the 11 cases of this kind described in the last five years the correct diagnosis had only been made after autopsy, drew attention to the recent work of Austin (1957) who reported 5 cases of the metachromatic form of diffuse sclerosis which had been diagnosed during life by the detection of abnormal material in the centrifuged urine sediment. Brain and Greenfield (1950) felt that/

that ~~the~~ late infantile metachromatic leucoencephalopathy should be separated from 'Schilder's disease' but at the same time they conceded that "an atypical sporadic case of Schilder's disease, beginning at the age of 2 or 3, presenting with disturbance of motility and running a subacute course", might be difficult to distinguish from it. Jefferson (1958) said, indeed, that the juvenile forms (of Scholz) may not be sharply divided from the late infantile metachromatic leucodystrophic forms of the disease and it may well be that the distinctive clinical features of the type of case under discussion derive from the distinctive developmental background of the age group affected rather from any essential difference from 'Schilder's disease'.

The neurological symptoms in the present case will now be discussed, individually, in greater detail from this developmental point of view:-

(1) Motility deterioration. The early cephalo-caudal maturation of motility had been normal. Sucking, grasping and groping, anticipatory movements preparatory to being picked up, raising of the head, sitting up and crawling had all occurred at the normal times and the child, who had made her first attempts at walking at $6\frac{1}{2}$ months, had initially, made further progress towards standing up and walking without support. Indeed, the slowing up, at 9 months, of the terminal stages of this process of motility-maturation did not immediately become severe enough to prevent the infant from almost achieving, at the age of 15 months, the ability to stand erect and to walk/

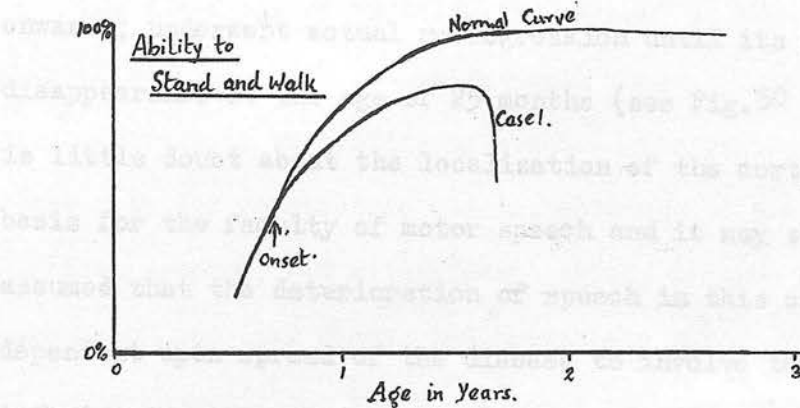
walk unaided (see Fig. 47).

Nevertheless, this slowing up passed quickly there: after into an actual retrogression and disappearance of such walking ability as had already been acquired. It was associated, at first, with a flaccid talipes valgus (more marked on the left in this right-handed infant) and, subsequently, with a hypotonicity which spread to affect the lower limbs, trunk, upper limbs and neck in a sequence which reversed the normal cephalo-caudal sequence of motility development so that the infant became progressively unable to stand, to crawl, to sit up or to hold up the head. Now, normal achievement of the ability to stand and to walk erect unaided is dependent upon the development of tone in hitherto hypotonic lower limbs. It is a specifically human achievement, dependent upon maturational tissue changes the localization of which is unknown but which may include the latest of the corticospinal fibres to myelinate - presumably those from the most anterior part of the premotor area for the lower limbs.

Achievement of the ability to suppress the infantile grasp reflex (whereby the hand is freed from a purely prehensile and locomotive function) is normally contemporaneous with achievement of the ability to stand and to walk erect and, although the neocortical apparatus for achieving this ability is also unknown, Adie and Critchley (1927) tentatively located it in the posterior superior frontal region. In this case forced grasping and groping were already present at the time when the patient was first examined and there is no means of knowing whether these reflexes/

reflected had re-appeared or whether they had never been suppressed.

(2) Speech & Imitation. Early speech development had been normal. The child had begun to speak at the usual time, had been able to say "Mama" and "Dada" at 9 months and, at 12 months, had been putting words together to form sentences. Indeed it was not until the age of 18 months, nine months after the onset of the illness, that the process of learning to speak began to slow down. It then became stationary for a time and, from 21 months



(3) Ascending Spasticity. It was not until the age of 22 months, more than a year after the start of the illness, that, superimposed upon the widespread state of hypotonicity,

Fig. 47 Diagrammatic representation of the mode of onset of the initial failure to learn to walk unaided and to stand upright in the case of the infant.

spread, again in a cephalo-caudal manner, to involve successively the lower limbs, trunk, shoulder girdles, upper limbs and neck, until the patient was finally immobilised in a state of complete rigidity.

(4) Paralysis. Paralysis seemed to be only a terminal feature and presumably indicated more widespread involvement of the brain - particularly of the so-called 'association areas'.

reflexes had re-emerged or whether they had never been suppressed.

(2) Speech deterioration. Early speech development had been normal. The child had begun to speak at the usual time, had been able to say 'Mamma and Dadda' at 9 months and, at 12 months, had been putting words together to form sentences. Indeed it was not until the age of 18 months, nine months after the onset of the illness, that the process of learning to speak began to slow down. It then became stationary for a time and, from 21 months onwards, underwent actual retrogression until its final disappearance at the age of 25 months (see Fig. 50). There is little doubt about the localization of the cortical basis for the faculty of motor speech and it may surely be assumed that the deterioration of speech in this case was dependent upon spread of the disease to involve the inferior frontal gyrus on the left.

(3) Ascending Spasticity. It was not until the age of 22 months, more than a year after the start of the illness, that, superimposed upon the widespread state of hypotonicity, spasticity began to appear. It appeared first in the legs (in association with Babinski's sign) and then gradually spread, again in a ^{caudo -}~~cephalo~~-cephalic manner, to involve successively the lower limbs, trunk, shoulder girdles, upper limbs and neck, until the patient was finally immobilised in a state of decerebrate rigidity.

(4) Dementia. Dementia seemed to be only a terminal feature and presumably indicated more widespread involvement of the brain - particularly of the so-called 'association areas'.

areas'.

Case 2. The Schoolboy.

In the case of the schoolboy, the insidious onset took the form of a phase of predominantly mental symptoms extending over a period of two years before the development of the cortical blindness and the increasing spasticity which led on to the fatal termination in decerebrate rigidity and dementia after a total period of about 32 months (Fig. 50)

The diagnosis of 'Schilder's disease' in this case, made clinically at an unusually early stage, was established progressively in the following manner. The presenting symptom at the psychiatric clinic, although it was not the earliest symptom, was a 'deafness' which, because of the absence of physical signs, had previously been considered to be psychogenic but which on closer scrutiny seemed to be, more in the nature of an auditory dysphasia. This symptom, having developed gradually and having been preceded (as became clear at the second interview) by a hitherto unnoticed alexia of even longer standing, suggested, in this right-handed child, a left-sided brain lesion such as a tumour. However, the subsequent development of a peripheral homonymous visual field defect which was unexpectedly to the left, suggested involvement of the right cerebral hemisphere also, while the occurrence of slight, rhythmic, involuntary, neck movements suggested an even more diffuse involvement affecting subcortical centres also. By this stage, the child was also showing some slight spasticity in the legs and it was at this stage/

stage that the tentative diagnosis of Schilder's disease was made. This diagnosis was strengthened by the subsequent emergence of true visual failure and by the later clinical features which conformed to the typical pattern~~s~~ as summarised by Brain (1948) and confirmed by the special investigations in hospital. Apart from the negative family history, the early alexia and the other early mental symptoms, to which special attention will shortly be paid, the clinical features of this case closely resembled those of the Scholz type of 'familial Schilder's disease' in which the child is said to be normal until the period between 8 and 10 years of age and deafness frequently to be the first symptom. This is said to be associated with aphasia, blindness and sometimes with optic atrophy; the pupillary reflexes and then the legs and the arms are progressively involved and there is mental deterioration with compulsive laughing and crying and involuntary movements of a choreo-athetoid type (Benda, 1952).

The neuropsychiatric symptoms in this case must now be discussed, from the developmental point of view, in greater detail:-

1. Dyslexia-alexia. Earlier mental development had been normal. The initial clinical feature, first noticed at the age of 6 years, was a slowness in the process of learning to read - a 'developmental dyslexia'. This symptom was not so severe, however as to prevent the child from being able, for a brief period, to read passably well before becoming, at 7 years 10 months, almost completely alexic.

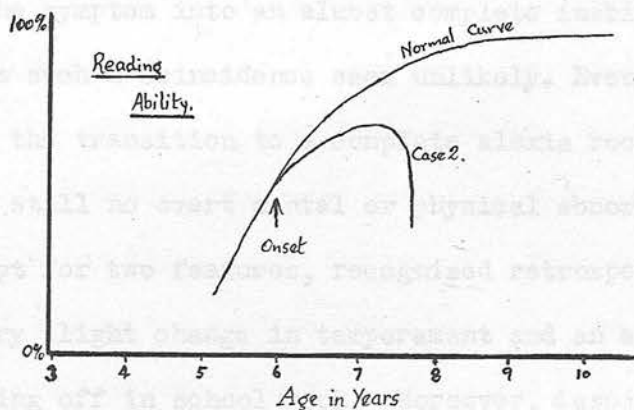


Fig.48 Diagrammatic representation of the mode of onset of the initial difficulty in learning to read and of the eventual alexia in the case of the schoolboy.

alexia. As the initial dyslexia was accompanied by no other indications of mental deterioration, it cannot be conclusively shown that the symptom, at this stage, was anything other than the relatively benign form of difficulty in learning to read which has been called 'specific developmental dyslexia' by Hallgren (1950). It is even possible that the latter condition was occurring in this child, by chance, at the time when he was about to develop 'Schilder's disease'. The early transition of the symptom into an almost complete inability to read makes such a coincidence seem unlikely. Even at the stage when the transition to a complete alexia recurred there were still no overt mental or physical abnormalities except for two features, recognised retrospectively, viz. a very slight change in temperament and an equally slight falling off in school work. Moreover, despite the early slowness in learning to read the child did in fact, achieve a limited degree of fluency in reading just before this ability was rather rapidly and completely lost - in the manner illustrated graphically in Fig. 48. Because there was loss of a partially acquired ability to read, not dependent upon peripheral factors but occurring as a result of brain disease, the inability to read was properly diagnosed at this stage as a 'secondary' alexia. It is of interest to note that the presence of the severe reading difficulty, associated, as it was, with normal object recognition, full visual fields and retention of general intelligence, almost escaped detection because the boy himself had not complained to the doctors of being/

being no longer able to read, the parents had not spontaneously disclosed the symptom (thinking it to be a matter of no significance) and a reading difficulty had neither been specifically enquired for nor excluded when he had attended previous clinics. At the psychiatric clinic the alexia was detected only at the second interview but its discovery led to the elucidation, for the first time, of the history of a preceding difficulty in the process of learning to read.

The early alexia in this case is of special interest for it does not appear to have been previously reported as the first symptom in Schilder's disease. Ceni's (1896) case, a girl of 9, may well have been dyslexic from the start of her illness but the record - 'konnte nicht mehr lesen' - does not exclude satisfactorily the possibility of a purely visual defect. Collier and Greenfield (1924) did not mention dyslexia as an early symptom although they pointed out that in some cases visual disorientation and visual agnosia (of which dyslexia may be regarded as a special instance) had in certain cases been recognised as having either preceded the usual cerebral blindness or as having existed in major degree when the blindness was as yet partial. It may be suspected, indeed, that the fact that dyslexia has so rarely been reported is by no means an indication that it is a rare early symptom in diffuse sclerosis for most reports give no indication of the symptom being specifically enquired for and in any case detailed clinical studies of such cases are usually instituted only when more or less serious visual defects, and/

and perhaps dementia, are already established. It is possible, indeed, that the symptom has been present at an early stage, though undetected, in many more cases than is at present realized. It may even be a common symptom in those cases in which the onset has been during early school days when the reading faculty has only recently been acquired for, in the following ten reported cases, which in fact had their onset during early schooldays, a perusal of the case records showed that in none of them could the symptom be excluded and also suggested that alexia might well have been present in any or all of them. In two cases it seemed rather probable, indeed, that dyslexia had been present, although there was no explicit statement to this effect.

Bielschowsky & Henneberg (1928) Case 1. - A boy aged 7, who developed impairment of hearing and spasm of the leg, was noticed two months later to be apparently completely blind. No information was given about reading ability.

Bielschowsky & Henneberg (1928) Case 2. - A boy of 10 developed a failure of 'word comprehension' and nine months later showed signs of failing vision attributed to optic atrophy. No information was given about reading ability.

Collier and Greenfield (1924) Case 1. - A boy of 7 developed failing vision over the whole visual field equally. No note was made as to whether reading ability was tested.

Ceni (1896) - A girl of 9 showed a slow onset with "confusion of mind" and loss of the ability to read.

Haberfeld and Spieler (1910). - A child of 7 developed failure of vision and inattention at school. 'Inattention' is perhaps the commonest explanation given for poor reading at school and suggests that the child may have been unable to learn to read - but this was not stated.

Siemerling & Creutzfeldt (1921) - A boy of 7 developed restlessness with disturbance of speech and gait. No account was given of the state of vision or/

or of the possibility of alexia.

Gasul (1930) - a boy of 8 developed vomiting, motor aphasia and a right sided hemiplegia. Reading ability was not mentioned. The onset had been sudden and there had been remissions (a so-called "chronic" form).

Meyer and Tennent (1936) Case 1 - a boy of 9 had had 'deafness' for 3 months and his vision was reported as being 'impaired'. Reading ability and the possibility of alexia were not discussed.

Stewart, Greenfield and Blandy (1927) Case 1. - a boy of 7 became dull, listless and rather 'deaf'. 3 months later his sight began to fail and he had weakness of the legs. When admitted to hospital 5 months later he was already blind and deaf. No information about a possible early alexia was given.

Brock, Carroll & Stevenson (1926). A boy of $8\frac{1}{2}$ became irritable, fidgety and showed a tremor. Memory and sight were impaired but details were not given of the nature of the visual impairment or of reading ability.

Secondary alexia, has, however, been reported in diffuse sclerosis at later stages of the disease - Walter (1918), for example, described the symptom developing a few weeks before the fatal termination in a physician suffering from the disease - but it is interesting that Collier and Greenfield (1924), commenting on Walter's case, not only did not mention the patient's alexia but remarked that there had been no visual changes.

Alexia is a topic which has been discussed extensively by Critchley (1954³) who did not, however, distinguish a 'primary', or developmental, form from a 'secondary' form. Critchley said that the first clinical reference to the subject was probably Lordat's autopathographical account in 1843 of his own transitory inability to read but that Kussmaul (1877) was the first to use the term 'word blindness' (Wortblindheit). Ferrier (1886) had pointed out/

out that the association between visual symbols and things signified was an indirect and comparatively loose one which, in alexic disturbances, gave way sooner, before a destructive or dissolving lesion of 'the centres of vision', than the more fundamental functions of visual perception and concrete visual ideation - an observation which is apposite to the case under discussion. It was Dejerine (1892), however, who gave the first clear and complete description of the condition, applying^{to}/it the term 'cecite verbale pure', and since those days many examples of alexia have been described and the condition has frequently been discussed from various points of view. Critchley (ibid) suggested that it could be approached clinically either as a visual agnosic, or as an aphasic disturbance. Although the condition of agnosia in the visual sphere necessarily implied the co-existence of dyslexia, the converse, Critchley pointed out, was not true, for dyslexia could exist without visual agnosia and had then to be regarded as a restricted type of visual agnosia or as a special instance of it. As an aphasic disturbance, alexia could be regarded as an impairment of symbolic thought and, thus conceived, it caused, in its mildest form, impairment of no more than the highest levels of the semantic or aesthetic appreciation of written language while at the other extreme, in its most severe form, so-called 'literal' alexia, it destroyed the patient's ability to recognise even single letters or numerals. In less complete forms of this 'literal' variety of alexia (as at the time of the first psychiatric examination/

examination of the case under discussion) the patient may still be able to recognise some letters of simple morphology (e.g. those of symmetrical form) or else groups of letters having special significance (e.g. the patient's own name or initials). In 'verbal' alexia, a form of intermediate severity, the patient, while able to read individual letters well enough, is unable to order the letters of words seen, into their correct sequence, sufficiently well to enable him to grasp the true sound pattern, and hence the meaning, of the word. In some patients, reading aloud may be possible, but not silent reading and conversely, in other cases, reading aloud may be possible, but only at the expense of understanding of meaning. Now, the concept of alexia is not universally accepted - the point at issue being the evaluation of peripheral factors (Klein and Harper, 1956). Thus, reading difficulties may often arise when, for ocular or central reasons, there is blurring or apparent movement of the print or when there is an undetected hemianopia - a state of affairs which may be particularly puzzling in the case of a lesion spreading deeply from the region of the angular gyrus into the optic radiations because in such a case an initial true dyslexia may become associated, at a later stage, with a hemianopia the discovery of which may cast unnecessary doubt upon the validity of the earlier observations. Such a sequence of events occurred indeed in the present case, for vision itself was unimpaired for a long time in the early stages and the first signs of peripheral visual field disturbance/

disturbance (visual inattention) on the left did not appear until the age of 7 years 9 months, long after the first reading difficulties. Central or paracentral scotomata may also give rise to a reading difficulty easily confused with true alexia, the distinction in such cases being comparable to Potzl's (1928) distinction between 'genuine optic agnosia' and what he described as 'certain asthenoptic phenomena due to lesions affecting the optic radiations'. Faust (1949), a pupil of Potzl's reported and discussed such a case of 'pseudo-agnosia optica', which presumably included a reading difficulty and which was due, in fact, to a paracentral scotoma. In the case under discussion central and paracentral visual impairment did not occur, however, until a very late stage in the disease. Reading difficulties, distinguishable at least theoretically from alexia, may also occur when the patient, because of a brain lesion, finds a multiplicity of visual stimuli distracting and an aggregate of visual material too much for him (Critchley, 1953). Again, such a mechanism may have been at work in the case under discussion because the patient had difficulty in listing correctly in a systematic order a group of objects seen together although he had been able to describe accurately individual objects seen separately. This difficulty in the temporal ordering of visual experiences may indeed be related to the very difficulty which Orton (1937) believed to underlie congenital word blindness, viz. a difficulty in repicturing, in the exact order, the constituent letters of/

of a word. Holmes (1950) explained an inability to maintain attention on one letter, if others were within vision, as being due to enfeeblement of the optic fixation reflex. Warrington and Zangwill (1957) made ophthalmographic eye movement records in a case of dyslexia and stressed the significance, for reading, of defective lateral eye movement. They discussed the relative parts played in reading difficulties by (a) visual field defects, (b) oculomotor derangement and (c) loss of recognition of visual symbols. The further fact that alexia probably does not exist in a 'pure' form (i.e. in the absence of other symptoms) and that most cases show, in addition, other parietal lobe symptoms, also calls for discussion because the present case was, on detailed examination, no exception. Alexia is commonly accompanied by impairment of visuospatial orientation and Martin (1954) said that since 1939 he had not seen any cases of pure word blindness in which there was not also a disturbance of visual space-appreciation of geometric type. Poor constructional ability, as in the present case, or actual constructional apraxia, may also be dependent upon such a difficulty in dealing with visual space. Alexia may commonly be associated with Gerstmann's syndrome and it was for this reason that attempts were made to test specifically for finger agnosia, acalculia, agraphia and right-left disorientation. Various circumstances however made it difficult, as the record explains, to decide whether or not Gerstmann's syndrome was present. Alexia is sometimes associated also with writing/

writing and spelling difficulties and both these difficulties were in fact present when the patient was first seen. Walter's case of diffuse sclerosis showed dysgraphia in which a disturbance in the ordering of letters was noticed, an observation which might relate its underlying mechanism to that suggested for verbal alexia by Orton (1937). The literature on Schilder's disease does not deal systematically with such parietal lobe symptoms. However, of Bouman's (1934) four cases of diffuse sclerosis his first one, a woman of 32 could not estimate distances and if she went to the door she did not know when she had reached it but as no mention was made of her reading ability this may well have been impaired. His second case, a man of 20, who had been mentally backward from birth, was 'only able to read slowly' but in this case it was, on the other hand, visuo-spatial difficulties which were not mentioned. His third case, a woman of 28, 'could not see well' and 'did not recognise a few objects shown to her' and if this was due to a visual agnosia it seems likely that she would also have been dyslexic although this was not stated. His fourth case, a man of 21, complained of a mist in front of his eyes, although nothing abnormal could be found on ophthalmic examination, and again there was no mention of the patient's reading ability although it was recorded that he had a difficulty in dressing - a symptom which also suggests a parietal lobe disturbance. All other case reports of Schilder's disease which have been perused have been found to be less illuminating on the subject/

subject of visuo-spatial difficulties than these cases of Bouman's. In the case under discussion the repeated construction and pulling down of the hut in the garden may have represented a reassuring defence against an incipient failure of constructional ability and may, indeed, have been an example of the condition which Critchley (1953) called 'katapraxia' and ~~and~~ which he quoted Pineas (1931) as picturesquely labelling the 'Penelope syndrome'. Moreover, the tendency of the boy, invariably to approach the examiner so closely as to be touching him, itself suggested a difficulty in judging distance. The association of alexia with defective colour appreciation is well known (Holmes, 1950), and Potzl believed that alexia and colour agnosia were always combined. Unfortunately, colour appreciation was not investigated in this case.

The first record in the literature of secondary alexia in which anatomical evidence about the site of the lesion was available was that of Broadbent (1872) when the symptom was ascribed to a lesion affecting the angular and supramarginal gyri on the left. Dejerine considered that there was in fact a centre for visual images in the angular gyrus and several other authors placed a word-seeing centre in or near that region. Oppenheim (1911) said that the memory pictures for written characters were apparently situated in both vision centres but he also said that in order to set these to work and to convert them into reading most people had first to produce the corresponding word sounds. When Oppenheim said that alexia usually occurred/

occurred in combination with sensory aphasia he said that the alexia in such cases was the result of injury of the 'centre for sound formation', a view which is of interest because although in this case the alexia was associated with a demonstrable sensory aphasia when the child was first seen at the clinic, the history showed that the first indications of sensory aphasia had not begun to appear until the alexia was already severe. In this respect the findings in this case therefore did not altogether confirm Oppenheim's dictum. Kleist assumed that there was a 'Lesenzentrum' in the angular gyrus or the adjacent second occipital gyrus on the left and also said that it was necessary to assume the involvement of callosal fibres from the right side. Others have maintained that a special centre for the formation of letters was located in the angular gyrus. Brouwer (1936), however, thought that the angular gyrus was not to be regarded as a word-seeing centre although it might be a nodal point through which passed impulses, of visual and other origin, which served the faculty of reading. Holmes (1950) suggested that the visual impulses on which reading depends may be differentiated and spatially segregated in the occipital lobe before they are transmitted to the appropriate association area which, as Brouwer had suggested, probably existed in the neighbourhood of the left angular gyrus. Holmes said that pathological changes in alexia were most commonly found in the left occipital lobe, chiefly in its basal part, and that they usually involved the lingual and/

and fusiform gyri. Sometimes the lesion was limited to the subcortical region and in others it extended into parieto-temporal gyri. In several cases the medial surface of the occipital lobe was involved. Bastian distinguished between a parietal and an occipital alexia. Other case reports have seemed to suggest that alexia invariably indicated disease of the angular gyrus in the dominant hemisphere (or else in the fusiform gyrus) and Henschen even spoke about 'angular aphasia'. According to Critchley, in a large series of cases it has been found that lesions giving rise to alexia may be much more widespread. They may chiefly affect areas merely contiguous to the angular gyrus and in some cases the angular gyrus itself may actually be spared. Indeed, in people who depend upon being able to read aloud to themselves, a lesion of the motor speech centre (Broca's area) would be sufficient to give rise to dyslexia. Neilson went so far as to say that alexia may result from a lesion anywhere from the occipital to the frontal lobe. Although it seems clear, therefore, that the hypothesis is no longer tenable that alexia is the specific consequence of disease of the angular gyrus the nodal significance of this region for the function of reading cannot, however, be nullified.

2. Dementia. Originally, the child was stable and of normal intelligence and it is of interest to note that he continued to show intellectual development even during the period when his specific and isolated difficulty in learning to read was becoming more apparent. The first/

first mental change was a slight alteration in temperament which began to appear when the boy was about $7\frac{1}{2}$ years old. It was, for long, an extremely insidious change, the child merely having occasional unexplained tearful attacks and becoming rather more passive, sensitive, and shy. It was not until some months later that he became, to those who knew him well, more clearly unstable emotionally - the change of school being offered as a psychogenic explanation of this change. Severe intellectual deterioration only set in at a very late stage, when the patient was already suffering from aphasic-agnosic disturbances and indeed it may have been dependent upon these as much as upon more widespread involvement of the brain. At 8 years and 5 months he became very irritable at all times, destructive of his clothing, and prone to laugh a great deal at night time for no reason - a feature recalling to the mother the fact that as a baby he had been described as 'a great laugh'. Terminally the emotional instability was replaced by a state of apathy passing into stupor. It is difficult to attribute these mental changes to changes in any particular region of the brain.

3. Auditory failure. It is interesting that in this case, the hearing difficulty developed, at the age of 7 years 10 months, distinctly later than the initial dyslexia for Oppenheim (1911) had said that the symptom of alexia usually occurred in combination with sensory aphasia. Auditory failure was indeed the first symptom for which medical advice was sought. At first, because of/

of negative otological and neurological findings, the 'deafness' had been attributed to psychogenic causes. At the psychiatric clinic, a plausible psychogenesis was forthcoming but even during the first psychiatric interview the speciousness of this psychogenesis became apparent as it became clear that the child's hearing difficulty was mainly of an aphasic nature distinguishable from true deafness of either organic or hysterical origin. The child under discussion did not seem to be aware of his poor hearing and, indeed, was apparently under the impression that he was hearing and understanding correctly when in fact he was not so doing. Klein and Harper (1956) said that the word-deaf person behaved as if he were deaf but Freud (1953) pointed out that patients with auditory aphasia commonly believed that they were hearing and understanding correctly when in fact they were not so doing while truly deaf people, whether organically or hysterically so, normally give clear indications of awareness of their deafness. Klein and Harper's case of pure word deafness (reported without pathological findings) had felt at times that people were speaking too loudly and had remarked 'you feel it should be louder but when anyone shouts it is still more confusing' and it is interesting to note that the present patient, similarly, objected strongly to his mother shouting at him.

Impairment of auditory function has been recognised in the past as a comparatively early symptom of Schilder's disease for Stewart, Greenfield and Blandy (1927) pointed out that, in some cases, 'cortical deafness' preceded cortical/

cortical blindness while Collier and Greenfield (1924) mentioned the occurrence, also, of auditory disorientation (a feature which, incidentally, was suspected in this case). It is interesting to note that in all the childhood cases referred to above, "impairment of hearing" was mentioned specifically as an early symptom in four of them but in only one case was the hearing difficulty described explicitly as "failure of word comprehension".

The anatomical basis for auditory aphasia is not clear. Bramwell (1927) reported the case of a woman of 62 who had two successive cerebral lesions, after the first of which she had had a sudden sensory aphasia with paraphasia and after the second of which she had become completely deaf. Autopsy showed that the two upper temporal convolutions were involved on the left and, on the right, the upper and posterior part of the superior temporal convolution and the supramarginal gyrus. In the discussion which followed this report Adolph Meyer said that permanent deafness occurred only when the brain between the insula and Heschl's convolution (see Fig 20) was destroyed and thereby the whole afflux of the auditory fibres to the left auditory centre was cut off. Bilateral (vascular) lesions in the temporal lobes usually resulted in word deafness only. So-called pure word deafness without paraphasia had hitherto usually been attributed to bilateral lesions in which, however, deafness is not a feature. Stengel and Lodge Patch (1955) reported 3 cases of 'central aphasia' which involved an incomplete receptive aphasia modified by impairment of the/

the ability to focus attention on to word sounds made by others and with a consequent inability to repeat sentences. They considered it to be due to a lesion in the superior temporal gyrus with extensive change of the neighbouring parietal area.

(4) Visual inattention. The patient's tendency to bump into lamp-posts and to fumble for door handles on the left was first noticed at the age of 7 years 11 months and naturally suggested, retrospectively, an actual hemianopia. However, this was excluded at a much later date and probably there was only a qualitative visual defect to the left, a 'visuelle Funktionswandel' - indeed Critchley (1953) mentioned that with progressive brain lesions a state of 'visual inattention' may precede an actual hemianopia. It seems to have occurred later than the alexia but before the hemianopia. In this case, the visual inattention would also explain the patient's increasing tendency to trip over small objects and not to look out for traffic. Anatomically the symptom is said to have a basis in a posterior parietal disturbance.

(5) Motility disturbance. Occasional weakness in the leg and unsteadiness of gait were first noticed also at 7 years 11 months and were the only early features of disturbed motility. The upper limbs were not affected until a much later stage. Slight rhythmic retrocollic movements of the neck were noticed shortly after the patient was first seen at the psychiatric clinic but these persisted only for a short time. The features suggest that there may well have been, in this case, an undetected ascending hypotonicity/

hypotonicity analogous to, if less marked than, that seen in Case 1, and dependent upon ascending changes in the corticospinal tracts.

(6) Speech deterioration. Progressive lack of emotional control of speech with slowness and slight paraphasia were the earliest evidence, at 8 years 1 month, of involvement of the expressive aspect of speech function. The anatomical basis for such indefinite symptoms is uncertain but a disturbance in the inferior frontal gyrus may have been responsible although complete mutism was only very late in this case.

(7) Visual failure. True visual failure, as distinct from the earlier alexia and the visual inattention, also began at 8 years 1 month, and took the form of a peripheral field defect to the left advancing towards the point of fixation and resulting in an actual hemianopia with macular sparing. By the time that the left hemianopia was established, a peripheral field defect to the right was also found to be advancing inwards. However, the impression was that 'tubular' macular vision still remained even at 8 years and 4 months. These clinical features suggested that involvement of occipital lobe white matter on the right occurred first and was followed quickly by a similar involvement on the left with sparing, however, of the fibres representing macular vision. The eventual loss of macular vision was attributable either to the increasingly severe cerebral lesion or to a late lesion involving the optic nerves.

(8) Ascending spasticity. Not until the time when the left/

left hemianopia was becoming complete, at 8 years 3 months, did the patient begin to show slight but progressive stiffness of the legs. This led eventually to frank spasticity associated with Babinski's sign, first on the left (in this right handed child) and then on the right. The patient then gradually became immobilized in an attitude of decerebrate rigidity, the legs and ankles assuming, terminally, a position of hyperextension, while the elbows and wrists were flexed over the front of the chest. The anatomical basis for such decerebrate rigidity lies probably in involvement of the reticulo-spinal as well as the cortico-spinal tracts in the lateral columns.

(9) Terminal symptoms. The mother commented on generalised tactile sensory loss which she noticed when tending the boy. There were no epileptic fits at any time but in the terminal stages laughing and crying attacks at night time became prominent. Bladder control was lost only in the terminal phase.

Case 3. The Adolescent.

In the case of the adolescent, mental symptoms predominated to the end in an illness lasting for about 7 years. Clinically, apart from a few syncopal attacks (not suggestive of epilepsy) which the patient was believed to have had between the ages of 12 and 15, no symptoms were noticed until the age of 14 when he began gradually to suffer a change of personality characterised by emotional blunting and an incongruity of affect indistinguishable from that of hebephrenic schizophrenia. This feature became gradually more marked and completely overshadowed/

overshadowed a probable, if slight, intellectual deterioration. Mental symptoms, together with sudden intermittent conjugate glancing movements of the head and eyes to the side which were suggestive of auditory hallucinosis, were well established for about a year and a half before the slightest objective signs of organic nervous disease appeared. Moreover, the latter, on which the tentative differential diagnosis of diffuse sclerosis or diffuse gliomatosis was made, only became definite very shortly before the patient's sudden and unexpected death in status epilepticus on the eve of his twenty-first birthday.

The chronology of the patient's symptoms is illustrated graphically in Fig. (50) but they will be discussed individually.

(1) Dementia. Mental development during childhood had been normal. The onset of emotional blunting was extremely insidious but retrospectively there were indications of it from his last year at school (aged 14) although it only became socially obvious later on when he was in the army. Intellectual deterioration was not marked during the early stages and indeed was only deduced by detailed retrospective enquiries from the Army authorities and from those who knew the patient intimately. The initial blunting and incongruity of affect suggested early damage to prefrontal fibres while the slight intellectual deterioration suggested parietal lobe involvement. The ability to read persisted in this patient at least until he was 20 years 4 months and it was not possible, latterly, to/

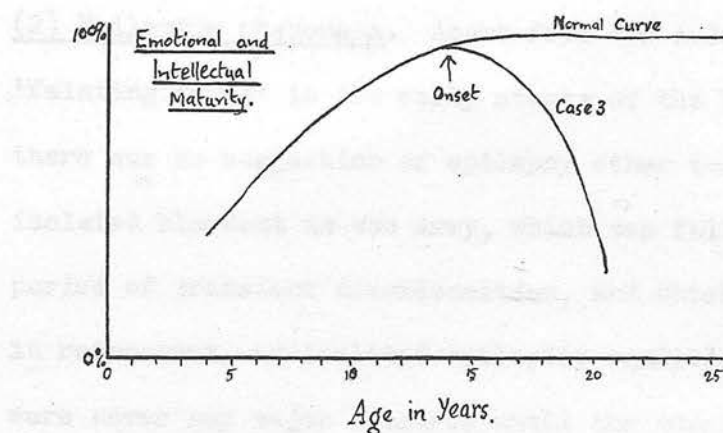
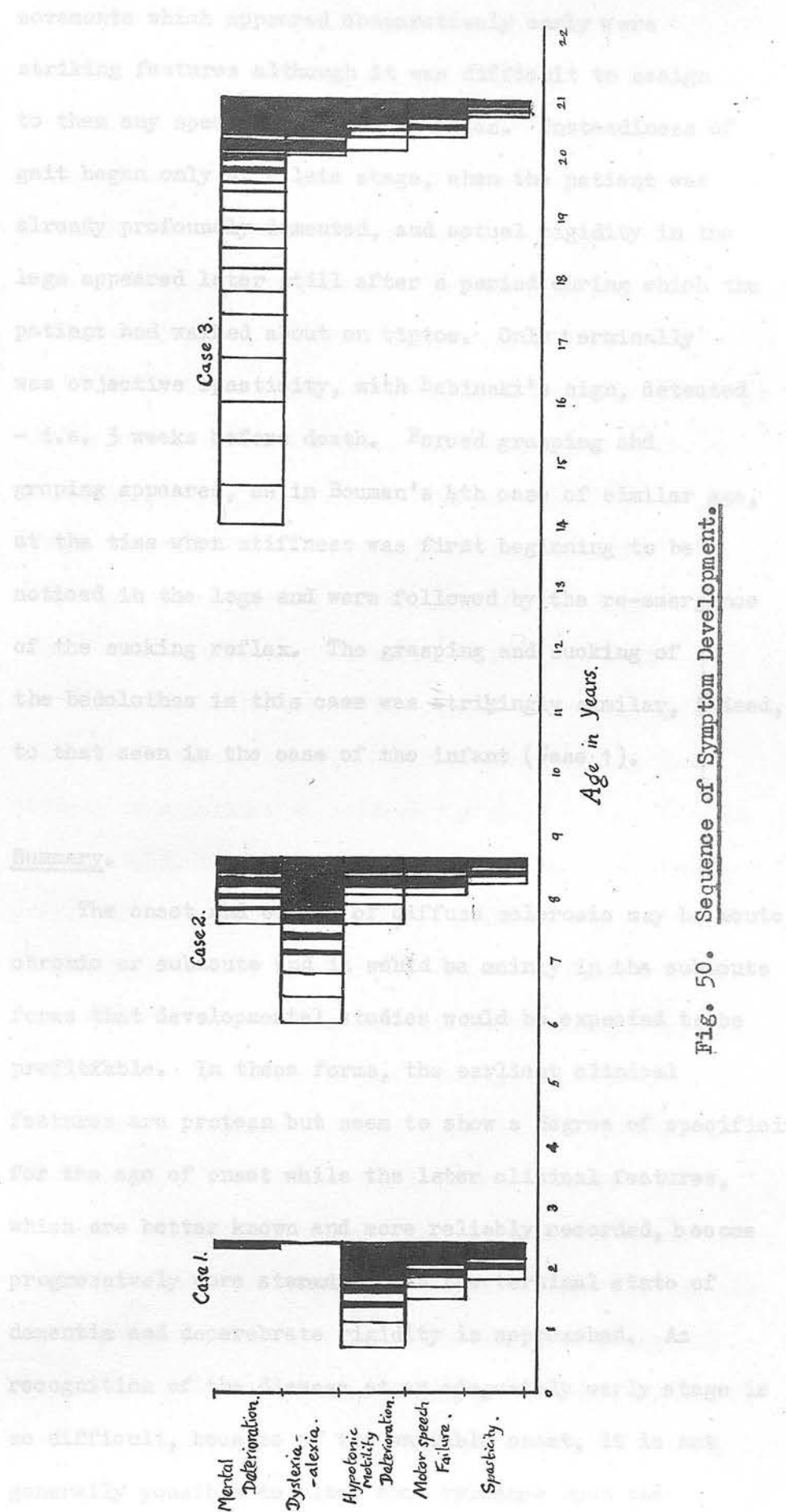


Fig.49. Diagrammatic representation of the mode of onset of the failure of emotional and intellectual maturation, with subsequent dementia, in the case of the adolescent.

to test for constructional apraxia. According to Wilson (1940), Ferraro described auditory hallucinations as occurring in the course of diffuse sclerosis but it is doubtful whether the present patient really suffered from these. The side to side glancing suggested, rather, pathological changes in the 'visual eye fields' in the parieto-occipital region and it may be noted that similar side to side glancing movements had been observed in Bouman's 4th case, who was of the same age as the present patient.

(2) Epileptic phenomena. Apart from the indefinite 'fainting turns' in the early stages of the illness there was no suggestion of epilepsy other than the isolated blackout in the Army, which was followed by a period of transient disorientation, and which was, probably, in retrospect, an isolated epileptic equivalent. There were never any major seizures until the terminal status epilepticus^{but}. The E.E.G. shortly before death had shown marked delta activity from the posterior parts of the brain. Winkelman and Moore (1939) said that convulsive seizures as a manifestation of diffuse sclerosis occurred less frequently in adults than in children. Gibbs and Gibbs⁷⁴ (1939) found E.E.G. tracings showing high voltage slow waves and associated small spikes in cases of supposed Schilder's disease not confirmed by autopsy while Cobb et al (1952) reported 3 cases of Schilder's disease diagnosed at autopsy which on the other hand had shown no spikes or transient activity in their E.E.G. records despite the fact that fits had been a feature of their illness.

(3) Motility disturbances. The side-to-side glancing movements/



movements which appeared comparatively early were striking features although it was difficult to assign to them any specific anatomical basis. Unsteadiness of gait began only at a late stage, when the patient was already profoundly demented, and actual rigidity in the legs appeared later still after a period during which the patient had walked about on tiptoe. Only terminally was objective spasticity, with Babinski's sign, detected - i.e. 3 weeks before death. Forced grasping and groping appeared, as in Bouman's 4th case of similar age, at the time when stiffness was first beginning to be noticed in the legs and were followed by the re-emergence of the sucking reflex. The grasping and sucking of the bedclothes in this case was strikingly similar, indeed, to that seen in the case of the infant (Case 1).

Summary.

The onset and course of diffuse sclerosis may be acute, chronic or subacute and it would be mainly in the subacute forms that developmental studies would be expected to be profitable. In these forms, the earliest clinical features are protean but seem to show a degree of specificity for the age of onset while the later clinical features, which are better known and more reliably recorded, become progressively more stereotyped as the terminal state of dementia and decerebrate rigidity is approached. As recognition of the disease at an adequately early stage is so difficult, because of the variable onset, it is not generally possible to place much reliance upon the accuracy of descriptions/

description of the initial symptoms in most case reports, especially when these are mental symptoms. Nevertheless, the clinical study of diffuse sclerosis from the developmental aspect must depend very largely upon adequate assessment of the earliest stages of the disease against the concurrent behavioural and psychological development of the affected individual.

In the three cases reported here, in which the onset was at widely different ages, the opportunity ^{was taken} ~~arose~~ of studying the initial symptoms from an unusually early stage. It was found, in fact, that the earliest disturbance represented a deterioration of those behavioural patterns which were, presumably, most actively undergoing maturation in the individual at the time. More specifically, they took the form, in the infant, of a failure to achieve the erect posture and to walk unaided, in the schoolboy, of a failure to acquire completely the incipient skill of reading and, in the adolescent, of a failure to complete that general maturation of the personality appropriate to his epoch of life in respect both of affectivity and intellect. The subsequent physical signs in all three cases, although they seemed to affect the non-dominant side first, were otherwise bilaterally symmetrical in their onset and spread and the terminal state of dementia and decerebrate rigidity was strikingly similar in all three cases despite the wide divergences of age at the time of onset.

PATHOLOGICAL ASPECTS.

Diffuse sclerosis of the brain (Schilder's disease) is characterised by a progressive demyelination, with subsequent sclerosis, of the whole, or of a large part, of the white matter of the cerebral hemispheres (the cortex being spared) so that at autopsy the brain comes to have an increased firmness, with slight atrophy, which on primary section, is commonly, but not always, clearly seen to be due to this massive demyelination and sclerosis of the central white matter. Histologically, the condition is characterised by demyelination of nerve sheaths and degeneration of axis cylinders, by a mesodermal reaction of inflammatory type with perivascular infiltration and by glial activity (Berliner, 1955). Oligodendrocytes may show satellitosis or mucinoid transformation, astrocytes may show change into the characteristic gemastete cells while microgliocytes form compound granular corpuscles (Wilson, 1940). In addition, there may be accumulation in the nervous tissues of myelin breakdown products and

However,
'prelipoid' substances. The recognition of the condition on the basis of these histopathological features, although usually straightforward, is sometimes as difficult as the clinical diagnosis because, as Bouman (1934) pointed out, the changes typical of diffuse sclerosis are not always recognised owing to the pathologist concentrating on the cortex and easily overlooking the changes in the white matter.

Now, the three cases originally described in detail by/

by Schilder (1912, 1913, 1924) showed such marked differences in their pathology that Lumsden (1951) took the view that Schilder's so-called 'encephalitis periaxialis diffusa' was really a heterogeneous group of conditions. Similarly, Greenfield (1958) pointed out that, although neurologists still tended to consider cases of diffuse sclerosis as variants of a single disease, there was a growing tendency among pathologists to separate those having different types of pathogenesis. He considered that there were four main groups viz. (1) the common, well-known, "sudanophilic" type, (2) the "Pelizaeus-Merzbacher" type (3) the "Krabbe" type and (4) the "metachromatic leucoencephalopathic" type. Lumsden (1951) believed that there were only two main varieties of true primary demyelinating disease in man, the polysclerotic and the leucodystrophic varieties, and that the commoner forms of diffuse sclerosis, as exemplified by Schilder's first case, came into the polysclerotic category while the leucodystrophic forms, characterised by metachromasia and the appearance in the brain tissues of prelipoid substances, were comparatively rare. Jefferson (1958), on the other hand, did not sharply distinguish the sudanophilic from the metachromatic leucoencephalopathic forms. R.D. Adams (Feigin et al., 1957) who pointed out that metachromasia was not an identifying characteristic of such forms, said that three other attributes identified them viz., defective formation or disintegration of medullated nerve fibres, conversion of the myelin into spheres /

and remnants of other shapes, and the fact that very little of the myelin seemed to be converted into neutral fats and cholesterol. Greenfield (1958) thought that the metachromatic leucoencephalopathic variety should only be diagnosed in cases in which the usual sudanophilic lipids were absent, except from the Virchow-Robin spaces.

Nevertheless, a close relationship of diffuse sclerosis to multiple sclerosis is shown by the fact that the massive lesion is often accompanied by subsidiary lesions in the brain and elsewhere in the nervous system and, conversely, by the fact that in cases of multiple sclerosis of late onset (after the age of 40) there is a tendency to run a progressive course and for there to be less dissemination of the lesions (Friedman and Davison, 1945). An 'intermediate' group of this kind was mentioned by Meyer and McLardy (1950) who said that three such cases (unpublished), falling in severity between ordinary disseminated sclerosis and Schilder's disease and occurring in the older age group, had been investigated in their laboratory and, in all three, severe organic dementia had developed several years before neurological abnormalities had become apparent - except for fits in one case. Poser (1957) also described two such transitional cases occurring in adult life and called them 'diffuse-disseminated' sclerosis. Furthermore, the demyelination and the sclerosis which are the outstanding features of both 'diffuse' and 'multiple' sclerosis, are common to a number of other conditions also and it was for this reason that Greenfield (1950) /

(1950) had previously suggested that there were perhaps no sharp dividing lines between the various demyelinating diseases generally despite the wide variability in the histological picture. According to Környey (1952) the 'encephalitis periaxialis diffusa' of Schilder has received general acceptance as 'an early stage' of diffuse sclerosis and McAlpine, Compston and Lumsden (1955) also said that they suspected that all the true demyelinating diseases were variants of the same basic pathological process. Einarson, Neel & Strömberg (1944), in their comprehensive studies of diffuse sclerosis, considered the various forms of the condition to represent essentially a single disease entity, due to the same aetiological factors acting with varying predominance. Einarson (1951) even claimed that on the one hand there were, from the "glioblastomatous" forms of diffuse sclerosis, direct transitions to diffuse glioma and to tuberous sclerosis while, from its degenerative familial forms there were transitions to amaurotic idiocy and to the lipoidoses in general. The pathological process in diffuse sclerosis, as thus broadly and comprehensively conceived, was briefly defined by Einarson and Neel, (1942), in the following terms:-

"Diffuse sclerosis constitutes a primary progressive process of demyelination and sclerosis of varying intensity, which spreads diffusely over the entire or over vast areas of the white matter of the two hemispheres and their great commissure, the corpus callosum. It may affect the two hemispheres equally or to a different degree, and it ordinarily spares the cortex and the subcortical arcuate fibres. The details of the tissue reactions, especially of the glia and the mesodermic vascular apparatus, as well as the formation of decomposition products, display marked quantitative variations within certain given limits".

The reconstruction of the earliest stages of the morbid process from the terminal anatomical picture is, as Wilson (1940) pointed out, beset with difficulties although this author himself commented that the fresh foci of the disease were pinker and that this pink colouration could be taken as indicative of the advancing front of the lesion (see Fig. 20). The question of the site of onset and mode of expansion of the earliest lesion has been discussed by other authors mainly in the course of attempts to explain the early visual failure in juvenile patients. In the course of such a discussion Collier and Greenfield (1924) drew attention to the significant fact that no instance of central scotoma from involvement of the extreme occipital pole had ever been reported and they believed that this fact confirmed that the formation of the initial focus was normally in the centre of the occipital white matter rather than at the occipital pole. Brain (1948) also believed that it was normally the white matter in the centre of the occipital lobe which was primarily affected and that the demyelination subsequently advanced towards the cortex. Einarson, Neel & Strömberg (1944) found that the fibres affected were preferably neocortical, those of the rhinencephalon and the commissures of the archipallium tending to be spared and it is usually suggested that the optic radiations are affected in a secondary manner, either by oedema or by the diffusion of a myelinolytic enzyme. The fact that in both the cases described by Collier and Greenfield (1924) the visual failure was observed to be over the whole/

whole field equally suggested to these authors just such a diffuse action in preference to the invasion of these tracts by an advancing discreet lesion. It is recognised, however, that wide divergences occur from the symmetrical, parieto-occipital type of onset, so typical of juvenile cases. While the brain changes are often asymmetrical or even predominantly unilateral, the question of the incidence as between the right and left hemisphere has not been discussed in the literature. Relative sparing of the subarcuate fibres during the corticopetal spread of the lesion has, in particular, been recognised as a striking characteristic of Schilder's disease, although it has also been emphasised that the escape of the subcortical layer of white matter is not absolute and is, according to Collier and Greenfield (1924), more apparent than real as the myelinated fibres in this region are, in fact, greatly impoverished by comparison with corresponding fibres in the normal brain.

It is well established that with progression of the disease white matter outwith the cerebral hemispheres, and in particular the white matter of the basal ganglia, cranial nerves, cerebellum, brain stem and spinal cord, may also be affected, and in a variable way. However, of all the extracerebral white matter tracts which may be involved, the optic pathways are perhaps of the greatest interest because they are so frequently affected in the demyelinating diseases generally and because there seems, indeed, to be, a distinct affinity for them.

Greenfield /

Greenfield (1954), who said that the optic nerves had only been affected in a few adult cases, and that blindness in children suffering from Schilder's disease seemed always to have been due to degeneration of the white matter of the occipital lobe, added that he saw no reason why there should be any restriction of such a kind. Optic atrophy, if infrequent, is indeed a recognised finding in Schilder's disease, the condition having been reported by Davison and Schick (1931) who enumerated several cases from the literature. Berliner (1935), commenting on optic nerve involvement in Schilder's disease, stated that no one had, at the time of writing, reported the presence of the disease in fibres of the retina itself, although this might happen in the event of a patch of myelinated nerve fibres being present and it was, indeed, for this reason that the retina in Case 1 was specially examined for myelinated nerve fibres. Winkelman and Moore (1939) also observed, in an adult case, optic atrophy which came on gradually and was definite before the patient's death. Involvement of the spinal cord is also of interest, the tracts which seem to be most frequently affected being the corticospinal tracts in the lateral columns.

In all three cases reported here there was a widespread involvement of the cerebral white matter in the demyelinating and sclerosing process typical of diffuse sclerosis while the three cases exemplified also the wide histopathological variations which characterise the disease. In the case of the infant the features were of /

of the comparatively rare diffuse progressive metachromatic leucoencephalopathic form while, in the case of the schoolboy, they were of the more common polysclerotic, sudanophilic, form and, in that of the adolescent, of the intermediate type. In each of these cases, comparative topographical studies of the demyelination were made with a view to attempting, in the light of the clinical features, reconstructions of the earliest stages of the disease.

Case 1. The Infant.

The brain of the infant showed no visible atrophy macroscopically, except for a slight falling in of Broca's area, but there was an increased firmness to the touch and on section, the white matter had a slightly more ivory appearance than normal. Microscopically, there was a wide: spread severe demyelination, with a striking accumulation in the white matter of P.A.S. positive material but with very little inflammatory reaction and no marked gliosis. The histological findings were such as to confirm the clinical diagnosis of the late infantile metachromatic leucoencephalopathic form of diffuse sclerosis.

Distal demyelination in individual nerve fibres and tracts, with neuronopetal spread is accepted as characteristic of the metachromatic leucodystrophic form of diffuse sclerosis but this feature was not clearly demonstrable in this particular case because the corticopetal spread seemed to have proceeded to completion in all fibres. The more gross topographical findings were consistent with the anatomical deductions from/

from the clinical findings. In particular, the initial bilateral flaccid talipes valgus suggested that the earliest involvement had been of the longest corticospinal fibres and the fact that it was rather more marked on the left was a slight indication of initial involvement of the non-dominant side. The fact that the next function to regress was motor speech suggested that fibres from Broca's area were the next to be invaded. The subsequent ascending hypotonicity suggested subsequent involvement of the shorter of the fibres of the corticospinal tracts in an ascending corticopetal manner and eventual subarcuate invasion of all zones of the cerebral hemisphere was indicated by the actual findings at autopsy. At lower levels, the optic nerves had been affected, but less severely than the cerebral white matter and presumably, therefore, at a later stage, and, in particular, the severity of the involvement of the nerve as a whole was not appreciably less than that of its maculo-papillary fibres. In the spinal cord, in addition to the severe involvement of the cortico-spinal tracts throughout their course, the reticulospinal tracts were also involved - but less severely and, presumably more recently.

The findings in the spinal cord in this case were of intrinsic interest in view of the fact that, according to Walsh (1957), the anatomical basis for decerebrate rigidity in man is still unknown. Walsh said that experimental findings with the monkey had suggested that the intense spasticity so often seen in chronic lesions of/

of the human cerebrum was determined by damage to extrapyramidal descending fibres rather than by interference with the cortico-spinal tract itself and, furthermore, that the evidence at present available suggested that the pathways from the reticular formation, which run in the anterior half of the lateral column (Hyndman, 1941), had an inhibitory action on spinal reflexes while the cortico-spinal fibres were responsible for the maintenance of spasticity. Further evidence in support of this view is therefore added by the actual clinico-anatomical findings in this case because the early ascending hypotonicity could surely be correlated with early involvement of the cortico-spinal tracts and the comparatively late rigidity with the later, less severe, involvement of the reticulo-spinal tracts (Fig. 9.)

Case 2. The Schoolboy.

In the case of the young schoolboy, the brain showed, macroscopically, slight atrophy and increased firmness and section revealed, in the central white matter of the occipital lobes, more or less symmetrical massive areas of translucent gelatinous appearance which only became visibly demarcated a minute or two after the section being made. Subarcuate invasion appeared to have taken place only anteriorly, however, in the association areas of the parieto-occipital region and in the insula, through the external capsule, while the internal capsule was not involved - a distribution which Greenfield (1958) described as being usual in the sudanophilic type of diffuse sclerosis. Subsidiary lesions were demonstrable in/

in the optic nerves, spinal cord and basal ganglia and microscopically the gross lesions were found to be regions of complete demyelination without gliosis but there were transitions to regions in which there was only early demyelination with various degrees of congestion and perivascular oedema. The features were, in fact, those of the Scholz type of Schilder's disease (Greenfield's 'sudanophilic' type).

The clinical findings suggested that demyelination had started rather earlier in the right, non-dominant, hemisphere than in the left while the actual post mortem findings confirmed a more advanced involvement of the right hemisphere. They indicated otherwise symmetrical bilateral foci of demyelination starting centrally in the white matter and progressing corticopetally with relative subarcuate sparing in all areas other than the parieto-occipital association areas and the insula. More specifically, the initial dyslexia-alexia, and the actual anatomical findings (Figs 20-21) suggested that the focus in the central white matter had involved first the fibres of the angular gyrus and part of the medial surface of the parietal lobe while the subsequent auditory disturbance, suggested that it had involved those of the lower part of the insula and the supramarginal gyrus at a later stage. The persistence of macular sparing of vision until a very late stage suggested that its obliteration may have been due, not to the cerebral lesion, but to that demyelination of the maculo-papillary fibres in the centres of the optic nerves which was found at autopsy. The ascending motility disturbance/

disturbance observed clinically in this case, consisted of a transitory phase of weakness in the legs followed later by a phase of ascending rigidity and, taken in association with the finding of involvement of the descending tracts of the lateral columns only extending as high as the brain stem and not into the cerebral peduncles or internal capsules, this suggested demyelination of the distal parts of the fibres of these tracts with incomplete spread in a cortico-petal direction. No differential involvement in the lateral columns, as between the cortico-spinal and the reticulo-spinal tracts, was, however, discernible.

Case 3. The Adolescent.

In the case of the adolescent, despite the tentative clinical diagnosis of diffuse sclerosis and the fact that at autopsy a bilateral depression of the occipito-parietal region of the brain was noticed which was very suggestive of atrophy of the underlying white matter, there was no macroscopical verification of the diagnosis on primary section of the brain. Moreover, the first histological examination was reported as negative and it was not until a year later, when reassessment of the microscopic sections was carried out, that careful histological studies confirmed the presence of ^{the} features of Schilder's disease and established the diagnosis. The findings showed that demyelination had been less severe than in the other two cases and more diffusely distributed, the picture being that of the 'intermediate' form. There was histological confirmation of involvement of both the/

the parietal region and the frontal region but unfortunately, shortage of histological material precluded accurate comparative studies of the various myelinogenetic zones, or of the optic nerves and spinal tracts.

The findings were, however, consistent with the tentative anatomical deductions from the sequence of the clinical symptoms. The early mental symptoms of blunting of affect and deterioration of the personality suggested early involvement of fibres of the prefrontal region while the scattered nature of the demyelination which was actually found suggested that this demyelination may have been mainly at the distal ends of these fibres and that the process had not coalesced to the stage of a gross, visible, focus and the very fact that this case was not immediately recognised at autopsy confirms the supposition that there was, in fact, no clearly demarcated lesion in the central white matter. There can be little doubt, however, that both the cerebral hemispheres were severely involved. There were no clinical indications of optic nerve involvement in this case. The very late occurrence of weakness and unsteadiness in the legs followed by ascending rigidity and Babinski's sign (appearing first in the left) suggested that an ascending involvement of the tracts in the lateral columns had been very late in its onset - but this could not be verified anatomically.

Summary.

Diffuse sclerosis of the brain is characterised by

a progressive demyelination and sclerosis of the whole, or of a large part, of the white matter of the cerebral hemispheres, the cortex ordinarily being spared. The histopathological features show marked quantitative variations and the diagnosis from the post mortem findings, although usually straightforward, is often missed. Reconstruction of the earliest stages of the pathological process from the post mortem findings is beset with great difficulties but, with the aid of anatomical deductions from the earliest clinical features, the attempt can and must be made if a developmental study is to be attempted.

In the three cases reported here the pathological findings were typical of the disease and exemplified the wide variability of the histopathological picture. More specifically, in the infant, they were those of the rare metachromatic leucoencephalopathic form, in the schoolboy, those of the comparatively well known sudanophilic type and, in the adolescent, those, probably, of the so-called 'intermediate' type. Attempts at reconstructing the earliest stages of the disease were made and the anatomical findings were consistent with deductions drawn from the clinical observations about the sites of the earliest lesions - confirming these in several particulars. In the case of the infant, the findings were consistent with early distal demyelination of, and subsequent corticopetal spread in, the corticospinal fibres for the lower limbs followed, successively, by demyelination/

demyelination of the inferior frontal gyrus (Broca's area), of the remainder of the fibres of the corticospinal tracts and, in due course, of the fibres of all cortical areas. At lower levels, there had been a diffuse, but less marked and therefore more recent involvement of the optic nerves and, in the spinal cord, the early involvement of the corticospinal tracts was followed by a later involvement of the reticulo-spinal tracts in the anterior halves of the lateral columns. In the case of the schoolboy, the findings indicated a bilateral onset in the centres of the occipital white matter, with complete corticopetal spread at first to the angular gyrus region and part of the medial surface of the parietal lobe but later to the insula and to the supramarginal gyrus. At lower levels, in this case, only partial involvement of other fibres seemed to have taken place, only the maculopapillary fibres of the optic nerves having been appreciably affected and only the distal portions of the corticospinal and reticulospinal tracts in the lateral columns. In the case of the adolescent, the findings were suggestive of only partial, and perhaps distal, involvement of individual fibres rather diffusely distributed throughout the brain and without the formation of a confluent, grossly visible, lesion in the centre of the white matter. In all three cases, although progression of the disease was otherwise symmetrical, there were some slight indications that the nondominant hemisphere had been first affected.

PATHOGENETIC ASPECTS.

The pathogenesis of diffuse cerebral sclerosis is little understood but the ways in which the terminal distinctive, if widely variable, pathological picture can be produced are almost certainly complex and the aetiological influences multiple. Any attempt at assessment of the pathogenesis must take account of (a) cerebroexogenous factors, (b) genetic factors, (c) constitutional tissue factors and (d) a possible developmental tissue factor.

A. EXOGENOUS FACTORS.

Known exogenous factors play an important part in certain specific forms of diffuse sclerosis and unknown factors perhaps some part in all forms of the disease. Their influence may be more or less remotely antecedent in contributing, during histogenesis, to those predisposing constitutional tissue factors which will be discussed below. On the other hand, they may have an immediate role in precipitating the initial demyelination of the disease.

The existence of an immediately acting exogenous factor is already proved, according to Einarson, Neel & Strömberg (1944), by certain features of the histopathology, notably by the perivascular character of the demyelination at the edges of the massive lesion. In their view, the exogenous factor, after passing into the cerebrospinal fluid from the blood vessels, reaches the tissues from the fluid in the perivascular fluid spaces and in the ventricles. Környey (1952), and others, believed that the massive lesion of diffuse sclerosis arose by the confluence/

confluence of many such perivascular lesions.

Now, the mode of incidence, in time, of a supposed exogenous factor in the demyelinating diseases is reflected in the clinical mode of onset and the subsequent course. For example, in multiple sclerosis, the clinical course suggests that the exogenous factor is characteristically abrupt in its onset, short lived in its duration and recurrent in its action (McAlpine, Compston & Lumsden, 1955). In acute forms of 'diffuse sclerosis', the onset is similarly abrupt, the illness running a comparatively rapid course, usually without remission, to a fatal termination. So-called 'chronic' cases typically exhibit similar, more or less acute, exacerbations with periods of arrest or remission suggesting the recurrent action of an exogenous factor. The onset in the subacute forms is, by contrast, insidious and the course steadily progressive, suggesting an exogenous factor of gradual onset whose action is maintained at a steady intensity or else is increased slowly. It may well be only with an insidious exogenous factor of this type that a possible influence of concurrent developmental processes in the tissues would be discernible.

The precise nature of exogenous factors in diffuse sclerosis commonly remains obscure although certain toxic substances are well known to be of prime importance in some forms of the disease. In a large group it may be that non-specific exogenous factors, varying in nature from case to case, are responsible and certainly no single exogenous factor has been incriminated as the initiator/

initiator of the early demyelinating lesions of this disease. Various possible exogenous factors have to be considered as follows:-

(1) Infection. It was the undoubted occurrence of an inflammatory reaction in both 'Schilder's disease' and multiple sclerosis which suggested the possible role of infection, a possibility which has been investigated by many workers with little success for no organism has so far been incriminated as specific for either disease. Adams, Blacklock and McCluskie (1924) attempted to transmit disseminated sclerosis to animals and, indeed, found spirochaetes in the ventricular cerebrospinal fluid of monkeys inoculated intraperitoneally with material from human cases of the disease. They did not, however, consider that these organisms were causally related to the disease.

Nevertheless, in Schilder's disease, Schaltenbrand (1927) believed that a brain which was congenitally predisposed succumbed to invasion by an ultramicroscopic virus, Levaditi (1930) thought that an oligodendrophilic neurotropic virus could definitely be incriminated, Ford and Bumstead (1929) reported two cases of Schilder's disease in one of which the illness had been ushered in by a severe attack of chickenpox and Gill and Richter (1932) seemed to assume infection to be an aetiological factor for they included Schilder's disease, multiple sclerosis and 'encephalitis disseminata' (of which they reported a case) under the heading of 'non-suppurative infectious encephalomyelitis'. Greenfield's (1933) first case of the 'late /

'late infantile metachromatic leucoencephalopathic' form of the disease became ill after whooping cough, his second case after measles and bronchitis while Brain and Greenfield's (1950) third case of that form of the disease followed a prolonged attack of whoopingcough at the age of 1 although their first and second cases gave no such history of a preceding infection. Winkelman and Moore's (1942) case of chronic progressive degenerative encephalitis had suffered from respiratory infection for one week before the onset of symptoms. Van Bogaert (1945) described 3 cases of an inflammatory cerebral disease he called 'subacute sclerosing leucoencephalitis', all of which were fatal within 3 to 6 months, but the condition he described was probably the same as Dawson's 'inclusion encephalitis', a definitely infective condition and Van Bogaert himself regarded the condition he had described as being distinct from other forms of 'diffuse sclerosis', although Lumsden looked upon Schilder's (1924) 3rd case as having been of this infective kind.

According to Davison (1950) an infective origin of diffuse sclerosis is not supported by the evidence, the inflammatory changes found in the disease being more convincingly interpreted as 'symptomatic' or 'reparative' and as resulting from the irritant effect of breakdown products of demyelination in the brain tissues. Einarson, Neel & Strömberg (1944) believed that this non-infective explanation of the inflammatory features did not rule out the remote possibility of a virus infection and that it was also possible that a variety of mundane infections elsewhere/

elsewhere in the body may indeed play a part by preparing the tissues of the patient for the selective action of a specific micro-organism proper to diffuse sclerosis.

(2) Allergy. Although Einarson, Neel & Strömberg (1944) believed that allergic inflammation in diffuse sclerosis could probably be assumed to be no more than an auxiliary factor, Kornyei (1952) believed that the basic mechanism was a neuro-allergic reaction. This view seems to be widely held for 'polysclerotic' disease generally and Smith, Espir, Whitty and Russell (1957) showed that the normal immunological processes were disordered in multiple sclerosis while McAlpine, Compston & Lumsden (1955) spoke explicitly of the possibility of a specific antigen-antibody union on the surface of the cell membranes of the oligodendrocytes with selective damage to these cells and to the corresponding myelin segments 'enclosed' by them. In allergic encephalitis, according to Lumsden (1956), there may be conjugation of the appropriate type of protein (derived from a source ~~of~~/exogenous to the brain) with a haptenic proteolipid of the patient's own nervous system giving rise to the formation of some type of antigen specific for myelinated nerve fibres. Lumsden (1957) said that there was some experimental support for the hypothesis of an immunopathological process in the brain with failure of acquired immunotolerances to myelin lipoprotein. Colover (1958) remarked that during recent years the concept that demyelination in the central nervous system may occur as the end result of an autosensitization process had been gaining ground and it may be that, in diffuse sclerosis, the/

the differentiating oligodendroglia becomes allergically sensitized locally and that the sensitized area subsequently succumbs to an allergic demyelination at a later stage in its development.

(3) Toxic factors. Mayer and Tennant (1936), who stressed the occurrence of gastrointestinal disturbances preceding the onset of 'Schilder's disease', believed this clinical feature to be very suggestive of a toxic factor and many toxic agents are already known to be capable of bringing about diffuse sclerosis in the brain. Verhaart (1941) stated that there was a type of toxic encephalopathy common in the Far East which 'simulated' diffuse sclerosis and Ferraro showed experimentally that potassium cyanide may have this effect. Einarson, Neel & Strömberg (1944) justifiably criticized the concept of 'simulated' diffuse sclerosis and maintained that widely different toxic agents merely acted as non-specific factors in initiating what was essentially one and the same pathological process. Innes (1934, 1939), who pointed out the similarity of 'swayback' in lambs to Schilder's disease, considered that the fact that the former disease could be prevented by the administration of copper to the pregnant ewes, suggested that, if swayback was not due to deficiency of copper as a trace element, perhaps copper afforded protection in some way from the action of a toxic agent such as lead. Davison (1950) said that it was reasonable to regard diffuse sclerosis as, in fact, a toxic process and Rossiter (1955) pointed out that the well known toxic demyelinating substances were metabolic poisons which inhibited//

inhibited the cytochrome oxidase-system. Walsh (1957) referred to the induction of demyelination by interference with oxidative mechanisms saying that many toxic agents were known to give rise to this and mentioning that it may be the result of interference with the non-specific cholinesterase enzyme associated with the myelin sheath. In the case of infantile spastic paralysis, he pointed out, was caused by a compound - tri-orthocresyl phosphate - which inhibited this enzyme.

(4) Lipolytic agents. Studies with exogenous lipolytic substances have thrown little light on the demyelinating disease. Einarson & Neel (1942) considered, however, that an endoenzyme, liberated from damaged oligodendrocytes and diffusing through the tissues, might well be a contributory factor resulting in the demyelination process spreading after it had once started. Such a cerebro-endogenous mechanism should be discussed more correctly and appropriately, however, under 'tissue factors'.

(5) Metabolic disturbances. Globus and Strauss (1928) attributed Schilder's disease to a sudden unspecified change in the normal metabolism of the nervous system due to some toxic agent or endogenous poison. Davison (1950) mentioned the possibility of a primary disturbance of lipid metabolism in the liver but Sperry and Waelach (1950), who showed that the synthesis of lipids occurred in the brain itself, argued from this that in the demyelinating diseases the dysbalance which occurred was not the result of a metabolic disturbance elsewhere. The diffuse progressive metachromatic leucoencephalopathic form/

form of the disease has been considered by some authors to be a form of lipoidosis but Leslie (1952) doubted this. Feigin, Wolf and Carter (1957) thought that the variability of the metachromatic substance in three cases of this kind which they had studied seemed to reflect a variability in the normal metabolic process leading to their formation and they considered it possible that the abnormal metachromatic materials did not represent an abnormal intermediate stage in myelin destruction but an aberrant intermediate product in myelin synthesis. Certain well known constitutional metabolic disturbances, such as phenylketonuric oligophrenia and porphyria, have been shown to have neuropathological features which are strikingly similar to those of diffuse sclerosis.

In phenylketonuric oligophrenia, one of the abnormal metabolic phenomena is known to be a tyrosine deficiency (Benda, 1952) and although it is not yet known what role tyrosine normally plays in the myelinogenetic function of the oligodendroglia Alvord, Stevenson, Vogel and Engle (1950) suggested that this was an enzymatic function, a deficiency of which caused a failure of protein metabolism, particularly of the neurokeratin proteolipids of the myelin sheath. The disorder was said to give rise, firstly, to an inefficient development of myelinated nerve fibres in the brain, and later, to an actual degeneration of these fibres with severe damage to the myelin sheath and a conspicuous accumulation of metabolic products in the white matter. Not only do the demyelinating lesions in this condition resemble those of 'diffuse sclerosis' but the behaviour/

behaviour patterns of those affected are, similarly, those of a degenerative psychosis becoming apparent at different age levels. While similar demyelinating lesions in the white matter of the brain occur in porphyria (Gibson, 1957), that disease runs a fluctuating course.

(6) Nutritional deficiencies. Meyer and Tennant (1936) and R.M. Stewart (1956) believed that nutritional deficiency might play a significant role in diffuse sclerosis. Lumsden (1951), who postulated that in the leucodystrophies the missing enzyme was a gene, believed that there was a deficiency of some prosthetic group and mentioned by way of analogy the role of a cobalt-containing crystalline red substance in subacute combined degeneration and the role of copper in 'swayback' in lambs. In view of the fact that vitamins are a source of coenzymes (David and Snyder, 1954) it may well be that nutritional deficiency plays some part in some cases in determining the predisposition of the white matter to demyelination and, more particularly, it is interesting to note that Strömberg (1957), on the basis of work reported by Glanzmann (1944), formed the clinical impression that the exhibition of vit B6 (pyridoxine) retarded the progress of the disease.

(7) Endocrine abnormalities. Endocrine factors were stressed by Baló (1943) who emphasised the importance of a hypophyseal cyst found at post mortem in a case of the 'concentric' type which he reported. He suggested that the demyelination and the neuroglial changes were due to the effect of an excessively active secretion which passed up through/

through the hypophyseal stalk into the third ventricle. Now, hormones, like vitamins, may be sources of coenzymes (David, & Snyder, 1954) and hormonal abnormality could, therefore, play a predisposing part in diffuse sclerosis analogous to that of a nutritional deficiency.

(8) Trauma. Trauma probably acts, if at all, as an entirely nonspecific agent.

(9) Psychogenic factors. As special attention has been paid in this study to the psychological aspects of diffuse sclerosis, reference must finally be made to the fact that Grinker (1950) seriously advanced, in a contribution to an authoritative symposium on the demyelinating disease, a theory which stressed the importance, in multiple sclerosis, of an exogenous emotional or psychogenic factor. According to this theory, the sufferer, who is said to be typically over-dependent upon the mother, succeeds in achieving a return, by means of the lesions of this disease to the unmyelinated (sic) state characteristic of the dependent infant. It seems hardly necessary to comment that the patchy demyelinating lesions typical of multiple sclerosis bear little resemblance to the unmyelinated state of infancy, and, while Grinker's theory might plausibly have been applied to Schilder's disease with its diffuse type of demyelination, this was a condition which Grinker himself did not in fact mention in this connection. Most other authorities attribute no significant role to psychogenic factors in the causation of diffuse sclerosis.

In none of the three cases under discussion was any/

any definite cerebro-exogenous factor identified. In particular, there was no evidence of nutritional deficiency, of trauma, or of significant psychological stress. Endocrine dysfunction could be excluded except for the resistance to insulin coma in the case of the adolescent in whom, indeed, a small, if probably insignificant, hypophyseal adenoma was found at autopsy. No contemporaneous infective processes were identified but it is possible that, in any of the three cases, infantile infections may have initiated allergic sensitization of the cerebral white matter and, in the schoolboy, chickenpox at the age of ten weeks is worthy of special note. No specific toxic factors were suspected in any of the three cases but in this connection, in the case of the schoolboy, the peculiar transitory greenish fluorescence noticed in the affected areas of the white matter some seconds after exposure to light is worthy of comment. It was conjectured at the time that this phenomena, which does not seem to have been previously described, may have been due to the transitory formation of coproporphyrin from its precursor cytochrome, under the influence of light (Klüver, 1944) the subsequent fading of the fluorescence being attributable to the breakdown of the newly formed coproporphyrin under the continued action of the light. Such a speculation, consistent with the occurrence of a biochemical block, of toxic origin, in the formation of coproporphyrin in the affected regions, would be in accordance with Rossiter's observation about the mode of action of demyelinating toxins.

B. GENETIC FACTORS.

Genetic factors have been suspected in certain specific forms of diffuse sclerosis for many years. Thus, the types of leucoencephalopathy starting in infancy and progressing for 2 or 3 decades and called 'spastic cerebral paralysis' by Pelizaeus (1885) and 'aplasia axialis extracorticalis congenita' by Merzbacher (1910) were immediately recognised to be heredofamilial. It was not long after Schilder (1912, 1913) had described his original cases that a number of authors began to draw attention to a familial incidence in some instances of 'Schilder's disease' also. Batten and Wilkinson (1914) described (but without postmortem findings) four adult cases of spastic disease which had started in infancy and which were clearly of a hereditary nature. Krabbe (1916) reported 'a new familial infantile form of brain sclerosis' describing a case of his own and four other similar cases, in which the onset was at about the 5th month and in which death took place 5 or 6 months later. In these cases there was destruction both of myelin sheaths and of axis cylinders. Bielschowsky and Henneberg (1928), who described two brothers who developed the disease in childhood, considered the hereditary forms to be distinct from the inflammatory forms. Symonds (1928) published a case in which there was a clear familial incidence and he mentioned also, incidentally, that a brother of the boy he described had shown the occasional temporary arrest of the condition to which Marie and Foix (1914, 1927) had drawn attention. Meyer and Tennant (1936) reported/

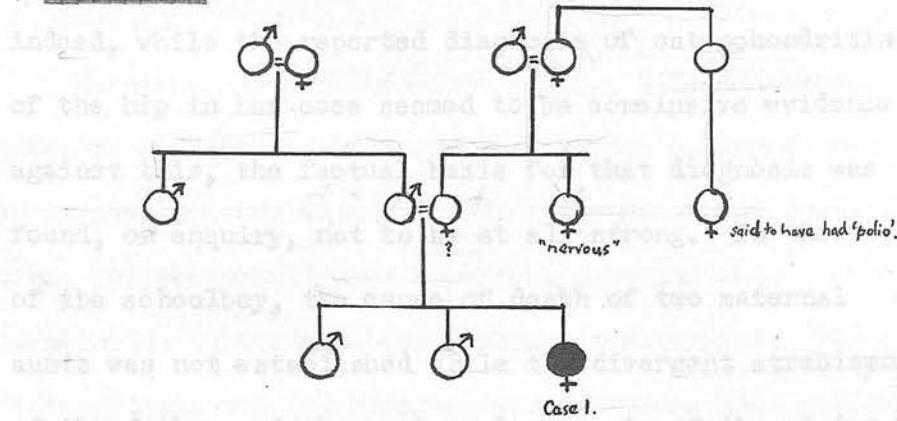
reported 'Schilder's disease' in an interesting family several members of which were affected. Ferraro (1937), Scholz (1925), Van Bogaert and Bertrand (1933), Habersfeld and Spieler (1910) and others also described a familial incidence. Einarson, Neel & Strömberg (1944), who carried out detailed genetic studies of several families affected by 'diffuse sclerosis', concluded that recessive genetic factors were prominent and that the disease was related, genetically, mainly to (1) various neuro-psychiatric and osseous abnormalities (2) hereditary spastic spinal paralysis (3) disseminated sclerosis. They pointed out that there was now little doubt about the presence of an hereditary factor in multiple sclerosis, a question which has also been discussed by Hadley (1954), McAlpine, (1955) and others. It seems that in the demyelinating diseases generally genetic factors probably always play some part, and that there are insufficient grounds, therefore, for distinguishing sharply between familial and sporadic forms.

In none of the three cases reported here was there any definite family history of the disease. It must be noted, however, that it was not possible to obtain full information about several of the known relatives and also that the siblings of any of the patients may yet develop the disease. In the case of the infant, the fact that the mother believed that she herself had been affected in infancy with a walking difficulty similar to that of her child raised the possibility, of considerable theoretical interest, that she herself had suffered,

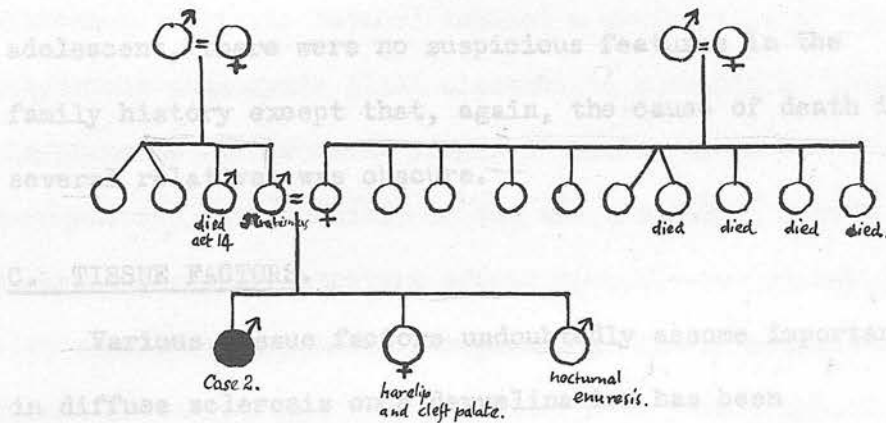
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Fig.51. Family Tree.

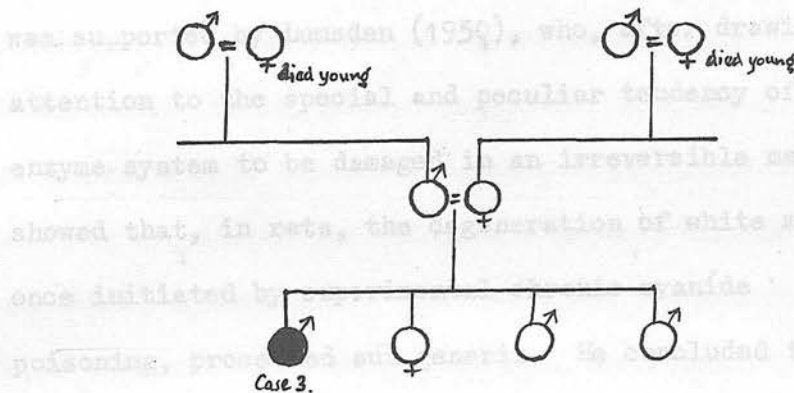
(a) The Infant.



(b) The Schoolboy.



(c) The Adolescent.



at the same age, from an abortive form of the disease and, indeed, while the reported diagnosis of osteochondritis of the hip in her case seemed to be conclusive evidence against this, the factual basis for that diagnosis was found, on enquiry, not to be at all strong. In the case of the schoolboy, the cause of death of two maternal aunts was not established while the divergent strabismus of the father and the nocturnal enuresis of the sister were certainly classifiable as "neuropsychiatric abnormalities" and the sister's cleft palate as a "related osseous abnormality". In the case of the adolescent, there were no suspicious features in the family history except that, again, the cause of death in several relatives was obscure.

C. TISSUE FACTORS.

Various tissue factors undoubtedly assume importance in diffuse sclerosis once demyelination has been initiated. Marburg's (1906) hypothesis that in the demyelinating diseases there was liberation, within the tissues of the brain itself, of a myelinolytic enzyme, was supported by Lumsden (1950), who, after drawing attention to the special and peculiar tendency of the myelin enzyme system to be damaged in an irreversible manner, showed that, in rats, the degeneration of white matter, once initiated by experimental chronic cyanide poisoning, proceeded sui generis. He concluded that, in diffuse and multiple sclerosis, contiguous regions of the white matter might similarly become affected as

a result of diffusion in the tissues of a myelinolytic enzyme.

Einarson, Neel & Strömberg (1944), believed that, in order to explain the wide range of tissue responses and, in particular, the relative preponderance of (a) demyelination, (b) accumulation of breakdown products and 'prelipoid' substances, (c) inflammatory reaction, (d) fibro-gliosis and (e) blastomatous or tumour-like reaction, it was necessary to postulate several distinct 'tissue factors'. In addition to their 'dystrophic tissue factor', which predisposed to the initial demyelination, their 'dyskatabolic tissue factor' implied a dysfunction of the mesodermic phagocytic glial elements as a result of which the products of the early stages of myelin decomposition were allowed to accumulate in the tissues and to have a disproportionately irritant effect upon the astrocytes with resultant excessive fibro-gliosis. Their 'histochemical tissue factor', which they admitted to be purely hypothetical, involved a reversal of the astrocyte response so that there was cell proliferation in inverse proportion to fibro-gliosis. Their 'dysplastic tissue factor' implied an individual inherent tendency of the macroglia to proliferation and blastomatous growth, i.e. a constitutional predisposition to tumour-like reaction, so that there was only a quantitative difference between diffuse sclerosis and diffuse gliomatosis. The fact that transitional forms occurred lent further support, according to these authors, to their hypothesis but it must be recorded that the 'globoid cells', considered to be blastomatous by/

by Einarson and Neel, were said, by Spielmeyer, not to be 'neuroglial', but mesodermal in origin (Greenfield, 1950). A failure of fibro-gliosis was ascribed to a 'dysreparative tissue factor' by Einarson (1951) who, in demonstrating yet another case said that it furnished a new strong argument in favour of the tissue factor hypothesis and that he then considered the dysreparative and dyskatabolic factors to be obvious realities. (Norman, 1947). There

Vascular tissue factors also play a role, as is seen in the perivascular disposition of the demyelination often to be observed at the edges of the massive lesion. Scholz (1925) believed that it was in the region of poorest blood supply that the myelin sheaths were most severely damaged. Bouman (1924), who pointed out that the cortex and subarcuate fibres were supplied by one group of surface vessels whereas the vessels supplying the central white matter formed a distinct group coming from the base of the brain, claimed that this disposition of the cerebral blood vessels played an essential part in that sparing of the cortex and of the subarcuate fibres which is such a striking characteristic of the disease. Kornyei (1952), however, who conceded that the difference of blood supply probably had a bearing on the sparing of subarcuate fibres, commented that it did not offer a complete explanation of the phenomenon and, indeed, the fact that cerebro-vascular disease is not normally a feature of Schilder's disease supports the view that Bouman's theory provides only a partial explanation of the subarcuate sparing. Vascular tissue factors seem to be of special importance in/

in some specific forms of diffuse sclerosis - for example in the case described by Frowein and Krucke (1951) in which the brain contained chalk-like deposits (Pseudokalkablagerungen) in the capillaries of the fourth layer of the area striata.

The central mystery of diffuse sclerosis is, however, the initial demyelination and the peculiar vulnerability of the myelin sheath (Norman, 1947). There seems to be virtual unanimity about the importance, for this, of some kind of inherent, constitutional, predisposition to dysfunction in the glial tissues of the brain. De Lange (1950) reported a familial case of Schilder's disease (of Krabbe type) in which she claimed that a hyperplastic abnormality of the glia represented the primary abnormality. Similarly, Davison (1950) spoke of a primary affection of the glia causing it to 'proliferate'. On the other hand, the growing recognition of the role of oligodendrocytes in the intracellular production of myelin and in the laying down and maintenance of the myelin sheath, together with the frequent finding of 'mucoid degeneration' of these cells in the disease, very naturally suggested the theory that the disease was due to an oligodendroglial dysfunction of a degenerative nature. Indeed, while a proliferative propensity of oligodendroglia is fully recognised, a degenerative reaction seems to be more characteristic.

The metabolic and enzymatic aspects of the oligodendroglial dysfunction in diffuse sclerosis have long been topics for investigation. Thus, Scholz (1934) described/

a disturbance in lipid metabolism in the glial cells and, although Bielschowsky and Henneberg (1928) ~~had~~ claimed to demonstrate the occurrence in the blood of abnormal lipids unsuitable for the formation or nutrition of myelin it is not so much abnormal lipids, or an excessive supply of them in the blood plasma, which is involved as a disturbance in the rate of lipid metabolism within affected glial cells (McAlpine, Compston and Lumsden, 1955). Lumsden (1951) said that in the leucodystrophies it could be postulated that the missing enzyme underlying the intracellular metabolic disturbance was a gene. Sperry and Waelsch (1950) pointed out, however, that the disturbance in the demyelinating diseases may not necessarily be chemical and that it may, for example, be a question of permeability of the cell membrane to the building stones of the lipid molecules. Also, the importance of distinguishing early, primary, degeneration of oligodendroglia from its commonplace disappearance from the demyelinated areas in the various kinds of demyelinating condition was stressed by Greenfield (1950) who said that there was not sufficient evidence to show that the oligodendroglia was involved in a primary fashion, or even at an early stage, in all forms of diffuse sclerosis. In the 'polysclerotic' forms Meyer and Tennant (1936) regarded the oligodendroglial dysfunction as probably being, not primary, but secondary to some other factor and McAlpine, Compston and Lumsden (1955), referring to the allergic theory, spoke of the possibility of a specific antigen-antibody union on the surface of the cell membranes of/

of the oligodendrocytes causing selective damage to these cells. The antithesis between 'primary' and 'secondary' dysfunction is avoided by the comprehensive 'tissue factor hypothesis' of Einarson, Neel & Strömberg (1944) in which they postulate a 'dystrophic tissue factor', considered to be a constitutional oligodendroglial 'insufficiency', which no more than predisposes to the development, under the influence of a cerebro-exogenous factor, of a trophic dysfunction of these cells. It is the induced dysfunction, in oligodendroglia, predisposed in this way, which is said to lead on to the swelling, degeneration and final disintegration of the affected cells considered to be the effective cause of the initial demyelination.

Now, in a number of brain diseases it has been held that the most vulnerable regions are those which, phylogenetically, are the most recent to develop. Jakob, for example, maintained that the regions chiefly attacked in general paresis and in senile dementia were those most recently acquired - i.e. the prefrontal regions (Economo, 1929) and similar findings have been claimed for certain of the presenile dementias. Moreover, Einarson, Neel & Strömberg (1944) found that the lesion in diffuse sclerosis was preferably neocortical and that the rhinencephalon and the commissures of the archipallium were normally spared while Mayer-Gross, Slater & Roth (1955) mentioned that, at least in adult cases, a lesion in the white matter of the prefrontal region was not uncommonly observed. However, in younger cases/

cases the lesion is typically much more variable, suggesting a wide variability, according to age, in the topography of the 'dystrophic tissue factor'. It is significant, perhaps, that the diseases mentioned above are affections, par excellence, of the mature adult brain and it may be that the variable picture in diffuse sclerosis at different ages is due to the fact that the latter is, by contrast, pre-eminently, and perhaps essentially, a disease of the immature brain.

In the three cases described here, no attempt was made to assess the various tissue factors which no doubt came into play after the initial demyelination. In order to explain the initial demyelination it was assumed that there was present a 'dystrophic tissue factor' - a constitutional insufficiency of the oligodendroglia - and, in particular, the striking topographical variability of this factor was noted.

D. A DEVELOPMENTAL TISSUE FACTOR.

The obvious concurrent myelinogenetic activity of the oligodendroglia in the diffuse sclerosis of early infancy is still quite often looked upon, as an accidental accompaniment merely confusing some essentially unrelated pathological process. In older patients, the concurrent maturational activity now known to be taking place in the oligodendroglia is not, as yet, generally acknowledged - still less is it widely accepted as an essential component in the 'Reaktionsweise' of the tissues in this disease. Nevertheless, Ferraro (1933) was inclined to think that/

that, in young animals, incomplete myelination and continuing myelinogenetic activity in the oligodendrocytes played some role in the relative vulnerability of the myelin sheath. Greenfield (1933), had suggested that there was, in the 'progressive cerebral sclerosis of infants', faulty development of those oligodendrocytes which were differentiated last. Ferraro (1937) also remarked that in the demyelinating diseases of man the patient's age at the time of their first appearance was one of the factors upon which the different types of these diseases depended. Similarly, Innes (1935, 1939) pointed out, in 'swayback' in lambs, that the state of myelin development at the time when the morbid process began had to be considered as a factor in influencing the course of the disease and he argued that it was unlikely that the pathogenesis of 'swayback' would be adequately understood until the myelination times of the fibre tracts in the lamb were better known. Greenfield (1958) while reaffirming that in the leucodystrophies demyelination was greatest in tracts that matured last, insisted that this remarkably selective loss was not seen in other forms of diffuse sclerosis and, the 'leucodystrophic' forms were also contrasted with the other better known forms of diffuse sclerosis, by McAlpine, Compston & Lumsden (1955), on the ground that demyelination in the latter did not progress symmetrically according to the inverse of myelin development, but began excentrically from a single focus and showed, subsequently, a different 'march'. An excentric focus and a variable 'march' are, nevertheless, susceptible of

a/

a developmental explanation provided that the ontogenetic and phylogenetic aspects are carefully distinguished and the variable maturational pattern of the brain tissues at different ages is borne in mind. Lumsden (1957) himself suggested that the solution of the whole obscure problem of the demyelinating diseases in man may prove to lie in the biology of the oligodendroglia and emphasised, in particular, the fact that there was some experimental support for the hypothesis that the special susceptibility of brain tissue to an immunopathological process was somehow bound up with the late development of myelin. It may well be, indeed, that the pathogenesis of diffuse sclerosis will be adequately understood only when the late myelinogenic activity of the oligodendroglia in the maturing ~~cerebral~~ cerebral hemispheres of the growing individual is better known and taken more fully into account.

The constitutional oligodendroglial 'insufficiency' assumed by Einarson, Neel & Strömberg (1944) to predispose to the onset of diffuse sclerosis is presumably itself the result of a genetic deficiency, or of a noxious cerebro-exogenous factor (e.g. allergic sensitization), or else of a combination of both, acting during the course of neurohistogenesis. Also, an early stage in the process of demyelination and perhaps the initial stage, is known to be the dissociation of lipid from protein as this occurs before the stage of chemical degradation of myelin (Adams, 1958). If, therefore, an essential role is to be ascribed to a specially vulnerable phase in the myelinogenic activity of the interfascicular oligodendroglia, this/

this role may be associated in particular with its activity in proteolipid formation. Furthermore, during the progressive lengthening of the double membrane during the helix formation which is now believed to take place in the formation of the myelin sheath, the proteolipid metabolism in the individual oligodendrocyte presumably rises progressively. A disturbance in the associated proteolipid metabolism, whatever its precise origin, would thus have progressively more severe manifestations as the myelin sheath approached maturity and the initial demyelination would therefore be expected to occur at those sites in which, at the time of onset of the disease, myelin sheaths were most nearly approaching their full maturity.

In the light of the developmental background which has previously been outlined, the above hypothesis would lead to a number of conclusions about the site of onset of the demyelination, about the mode of its subsequent march, about the march of the clinical symptoms and ultimately about the final topography of the massive lesion at autopsy. In particular, a noxious cerebro-exogenous factor acting diffusely over the whole length of the individual myelin sheath would show its first influence in the outer layer where myelinogenesis was still actively proceeding and would progress inwards to affect the concentric layers of myelin successively. Also, it would initially give rise to complete demyelination at the distal end of the nerve fibre and the process would advance proximally towards the point on the axon, near the nerve cell, from which myelination normally starts and/

and from which the interfascicular oligodendrocytes begin their developmental migration. Moreover, in the demyelination of a specific myelinogenetic zone or unit, the demyelinating process would affect, first, the longer efferent fibres from that unit and this distal demyelination widely scattered, perhaps, in the brain or elsewhere, might well give rise to no grossly visible lesion. It would only be as the demyelination spread towards the site of origin of the affected fibres and as the individual fibres were congregated together in the central white matter, that, as a result of the neuronopetal demyelination which has been envisaged, the demyelination of individual fibres would coalesce and the gross appearance would be of a visible focus of demyelination forming in the central white matter. Furthermore, it would only be after the longer efferent fibres of such a myelinogenetic unit had been affected in this corticopetal manner, that, in due course, the shorter association fibres would be affected - and only finally would the subarcuate fibres and intracortical fibres be invaded (see Fig. 52). It would be further supposed, on the tentative supposition mentioned above, that the myelination of the non-dominant hemisphere lags slightly behind that of the dominant hemisphere, that the non-dominant hemispheres would be the earlier to be affected, giving rise to an 'excentric' onset of the disease.

The relative predisposition of the individual cortical myelinogenetic units, furthermore, would show a pattern varying with the altering pattern of myelinogenetic activity/

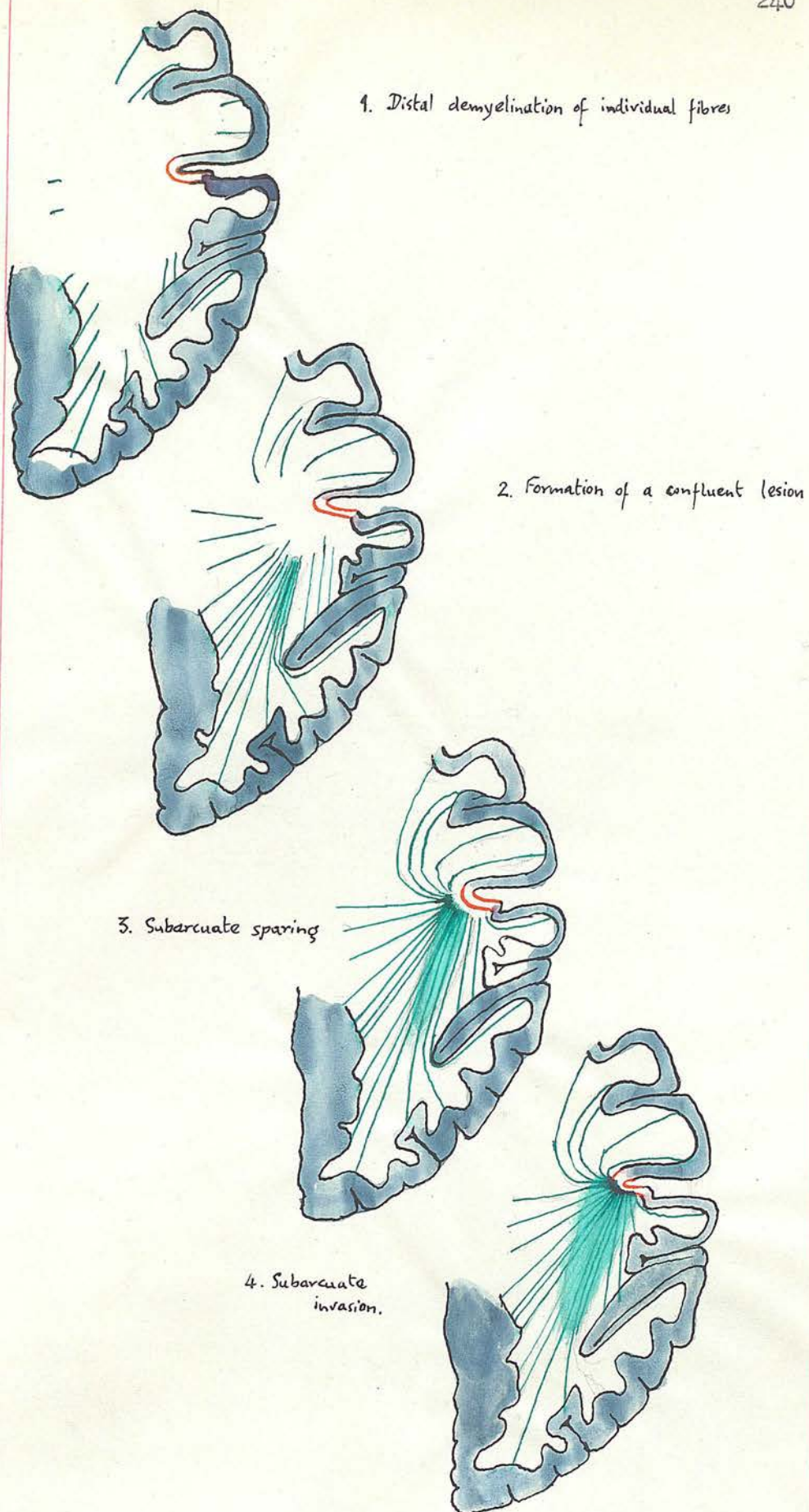


Fig.52. Diagram illustrating hypothetical corticopetal demyelination of the efferent fibres from a specific myelinogenetic zone (indicated in red).

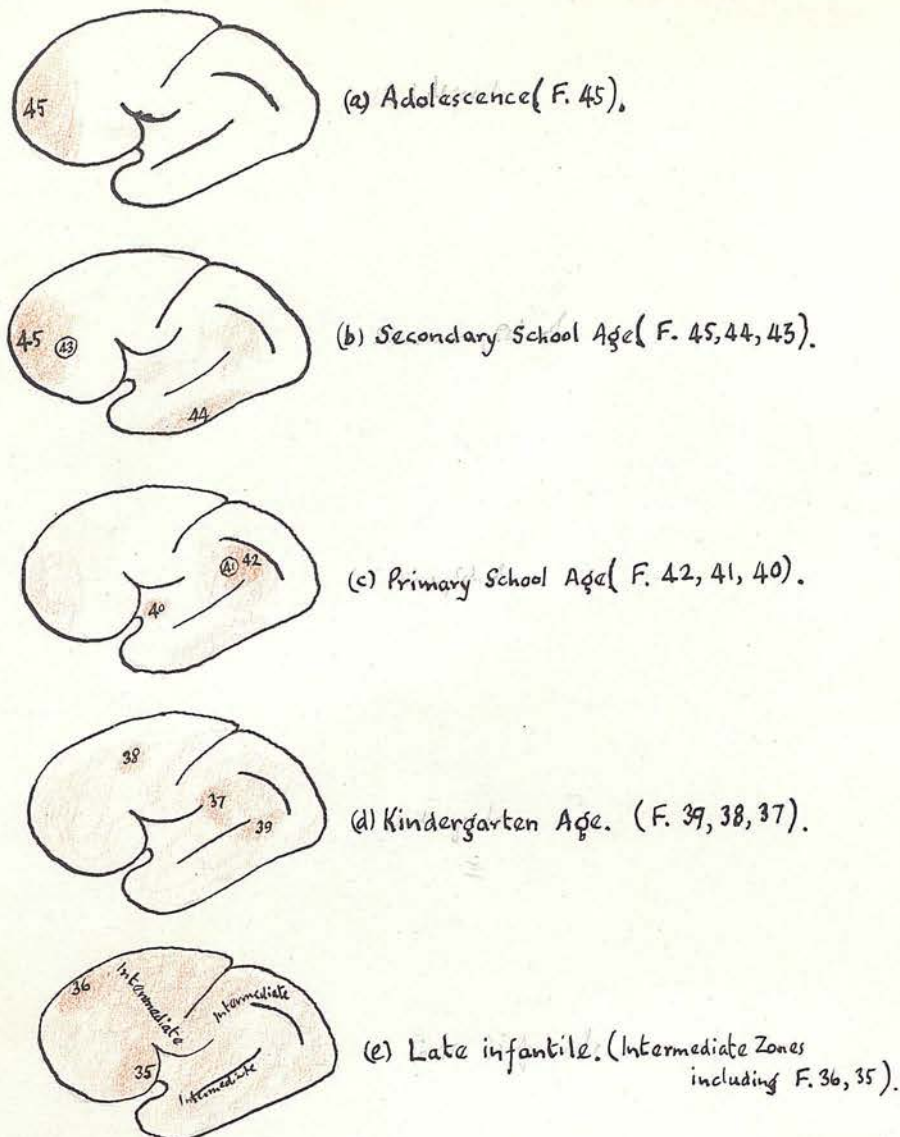


Fig. 53. Diagram indicating the suggested sites of the specially vulnerable myelinogenetic zones at different ages.

activity in the brain in the course of individual development and, taking into account the prolonged maturation of the later intermediate and terminal myelinogenetic zones of Flechsig during the period of infancy, childhood and adolescence, the origin and march of the demyelination would be expected to vary accordingly. In general, as the patient's age varied from adult life to infancy, the site of the initial lesion would vary from the/

the latest to the earliest of Flechsig's myelinogenetic zones. More specifically, with an onset in adult life, it would be the last of Flechsig's myelinogenetic zones, i.e. F45 in the prefrontal region, which would be the zone to be initially involved. Moreover, due to the fact that most of the efferent fibres of the terminal myelinogenetic zones are association, rather than projection, fibres, their demyelination, occurring distally to begin with, would be widely scattered in other areas of the cerebral hemispheres, 'diluted' as it were amongst normal, unaffected fibres and, indeed, the process may perhaps never spread far enough corticopetally to form a macroscopically visible focus. With an onset in adolescence the main incidence would include some of the preceding 'terminal' zones (i.e. areas F43 - 45). In juvenile cases a group of the earlier of the 'terminal' zones would be first affected and the demyelination, which would tend to spread further corticopetally, would be limited to those few of Flechsig's areas which would be actively maturing at the time. With an onset in infancy the numerous and extensive 'intermediate' zones (F18 - 36) would be first affected, with rapid corticopetal spread, and an equally rapid extension to the actively maturing primordial and terminal zones also, so that there would, in fact, be very few actively myelinating fibres in the brain unaffected. With a prenatal or paranatal onset of the disease the 'primordial' /

'primordial' zones (F1-17) would be mainly attacked.

Continued operation of the demyelinating mechanism would result in the eventual appearance of obvious demyelination in the phylogenetically older white matter tracts and dissolution at these lower levels would take the form of an increasingly stereotyped reversal of myelinogenesis. In particular, in the basal ganglia, the white matter of the (neocencephalic) caudate nucleus would be expected to be affected comparatively early because this region myelinates comparatively late. Of the cranial nerves which would be eventually affected, involvement of the comparatively late-maturing optic nerves and tracts (particularly the maculo-papillary bundle) would be expected to be the first. In the spinal cord, involvement of the corticospinal tracts (which means, in fact, involvement of the long fibres arising from Flechsig's 'primordial' and 'intermediate' myelinogenetic zones of the cortex) would be expected to occur before involvement of the more primitive of the spinal tracts. Moreover, commencing distally it would be those fibres of the corticospinal tracts which are concerned with the motility of the lower limbs which would be involved initially, and only later those concerned with the motility of the upper limbs, because the myelination of the former is normally achieved later than that of the fibres for the upper limbs. Furthermore, while involvement of the corticospinal tracts would be expected to occur in adult and adolescent cases only at a comparatively late stage in the disease, it would occur at a rather earlier stage in the disease in juvenile cases/

cases while in infantile cases it would occur earlier still. Also, the reticulospinal tracts would be involved later than the corticospinal and there would be a temporal dissociation between the involvement of these two tracts in the lateral columns which would be progressively more marked in the younger subjects.

Now, Holmes and Young (Rossiter, 1955) reported that, during the demyelination of the individual nerve sheath, myelin, in fact, disappears first from the outer layer. Also, according to McAlpine, Compston and Lumsden (1955), the march of demyelination shows precisely such a neuronopetal reversal of the normal neurofugal myelination of the individual fibres as has been suggested, at least in the leucodystrophic forms of diffuse sclerosis. The general susceptibility to nervous disease of the nondominant hemisphere has been frequently noted in the past since the comment of Scaliger, quoted by Sir Thomas Brown (1672) in his 'Pseudodoxia Epidemica',:-

'that Palsies do oftenest happen upon the left side if understood in this sense; the most vigorous part protecting it self, and protruding the matter upon the weaker less resistive side.....',

but the possible predisposing influence of cerebral dominance in diffuse sclerosis, in causing an eccentric onset and in determining which hemisphere is initially affected, does not seem, however, even to have been considered hitherto. Indeed in a perusal of case reports from the literature it was found that the handedness of patients was scarcely ever recorded so that it was impossible to investigate the question whether or not the/

the non-dominant hemisphere was normally involved earlier and slightly more extensively than the dominant - as would be expected on the present hypothesis. In adult patients, although the last of Flechsig's terminal myelination: genetic zones (F45) in the prefrontal region may be clearly affected in some cases, the findings in others are not so obvious, although they are often consistent with distal demyelination of affected nerve fibres from the prefrontal region, diluted amongst normal fibres, and with a failure of the demyelination to progress corticopetally to the stage of forming a grossly visible lesion in the centre of the white matter. The occurrence of a grossly detectable focus of demyelination in the central white matter, with corticopetal spread and relative sparing of the subarcuate fibres, is most clearly observed in the well-known juvenile forms. The relative invulnerability of the subarcuate fibres is also seen most clearly in such cases and it may be pointed out that the explanation of this subarcuate sparing on the present developmental hypothesis is consistent both with Einarson's (1951) view that the cerebral cortex and the subcortical association fibres

'constitute a separate histopathogenetic system, different from the commissural and projection fibres of the semioval centre'

and with the fact, which Einarson pointed out in support of this view, that, while sparing of this system occurs in diffuse sclerosis, the prenatal 'demyelination' of amaurotic idiocy is, by contrast, mostly confined to the/

the same system. A corticopetal 'march' of the disease may well be obscured, in infantile cases, by universal subarcuate invasion taking place before death with total involvement of practically all the affected fibres of the vigorously maturing brain. Finally, in cases having an origin paranatally or prenataally there seems indeed to be a comparative prominence of 'central' patterns affecting, mainly, efferent fibres arising from the primordial zones and descending into the internal capsules. Accounts of the involvement of the white matter at lower levels is of special interest from the developmental point of view in connection with involvement of the optic nerves and tracts because of recent advances in the study of the anatomy of these structures. Putnam (1933) and Franklyn and Brickner (1947), in discussing the pathogenesis of the plaques of demyelination commonly involving the macular fibres of the optic nerve, had suggested that thrombosis or vasospasm were responsible. Behr (1935) believed that the vascular anatomy of the intracranial part of the optic nerve was such that the fibres of the maculopapillary bundle would be more specifically exposed to the effects of ischaemia than the other fibres while Vail (1948) believed that the temporal side of the intraorbital part of the optic nerve which, in its distal part, includes the maculo-papillary bundle, was more liable than other regions of the nerve to the effects of ischaemia. However, recent anatomical studies of the capillary arrangements in the optic nerves have called these views very seriously in question and have/

have tended to emphasise the importance of the developmental status of the nerve fibres involved, rather than the anatomy of their blood supply. Blunt (1956) maintained in fact that there was no evidence for the thrombosis or vasospasm theory in the demyelinating diseases and Hobbs (1956) emphasised the fact that the maculo-papillary bundle, as it passed from the temporal side of the optic nerve at the disc to reach the centre of the nerve in its posterior part, appeared to be supplied with blood through a capillary network no different from that of the rest of the nerve and that, contrary to previously accepted views, it did not receive the preferential blood supply which the supposed existence of a central artery of the optic nerve had suggested. He said that not only would the theories of Putnam and Franklyn and Brickner now seem to be improbable with the capillary system which had been demonstrated but that such a capillary system would appear to be particularly vulnerable to the pressure of the generalised oedema resulting from the allergic mechanism widely thought to underlie the demyelinating diseases. He favoured, in fact, the conception of a greater inherent vulnerability of the more 'highly specialised' fibres comprising the maculo-papillary bundle, as compared with the vulnerability of the remainder of the optic nerve fibres. His conclusions were, in fact, in accord with the present developmental hypothesis which suggests that the optic nerves would normally be involved, sooner or later, in diffuse sclerosis but that the fibres forming the maculo-papillary bundle, which/

which appear to be the latest to myelinate and to mature, would be the most vulnerable to demyelination. Finally, involvement of the cortico-spinal tracts in diffuse sclerosis is also of special interest and although the clinical observation that the lower limbs are usually involved before the upper limbs has often been attributed to a gradual horizontal spreading forwards of the demyelination into the internal capsule, Greenfield (1958) pointed out that, at least in the common sudanophilic type, this did not happen. Indeed the caudocephalic spread of motility disturbance may be better explained by the fact that the maturation of the corticospinal fibres for the lower limbs occurs later than the maturation of those for the upper limbs and that it is for this reason that they are liable to earlier demyelination.

In all of the three cases which have been investigated here, the clinical and anatomical findings suggested that a developmental tissue factor, in the ontogenetic rather than the phylogenetic sense, had played a fundamental part. The earliest clinical feature in each case represented a maturational failure, with subsequent dissolution of the behavioural pattern most actively maturing at the time and the pathological findings were consistent with our imperfect knowledge of the structural basis in the nervous system for these behavioural patterns. More particularly the onset in each case seemed in fact to have been broadly symmetrical but slightly earlier and more marked on/

on the non-dominant side in each case. Initial demyelination of fibres at their distal ends, with proximal neuronopetal spread of the process, although widely accepted in the late infantile metachromatic form of the disease, was not actually demonstrated in the case of the infant but was seen in the case of the schoolboy in the purely distal involvement of the longer fibres of the corticospinal tracts. The formation of a macroscopic focus of demyelination in the central white matter of the cerebral hemispheres with corticopetal spread had apparently not advanced to the stage of a detectable focus in the case of the adolescent, but it was clearly seen in the case of the schoolboy although, again, it was not seen in the infant at autopsy presumably because corticopetal spread and subarcuate invasion had by then been complete in all the cortical areas. At lower levels, involvement of the optic nerves although not as severe as that of the cerebral hemispheres, was diffuse and clearly detectable histologically in the case of the infant, easily seen macroscopically but confined to the late-maturing maculo-papillary fibres in the case of the schoolboy, and probably minimal in the case of the adolescent. Motility disturbance occurred early in the case of the infant and the initial ascending hypotonicity was dissociated very clearly from the subsequent ascending rigidity, a dissociation attributable to comparatively early involvement of the late-maturing cortico-spinal tracts in contrast to a comparatively late involvement of the more primitive reticulo-spinal tracts. Motility symptoms in/

in the schoolboy occurred at a later stage in the illness and, although dissociation between early hypotonicity and subsequent rigidity was probably present here also, it was not an obvious feature. Motility deterioration in the adolescent developed very late and any dissociation between initial hypotonicity and subsequent rigidity, if it occurred, was not detected.

Case 1. The Infant.

The findings in this case were consistent with initial distal demyelination of, and corticopetal spread along, the longest of the corticospinal fibres (? from Flechsig's intermediate area 36), followed successively by involvement of Flechsig's area 35 (Broca's area), of all his intermediate and primordial zones and, before death, of his terminal zones also. Corticopetal spread and subarcuate invasion had clearly been complete in all areas. At lower levels, the optic nerves had been affected diffusely, without any differential preference for the later maturing maculopapillary bundle being detectable at autopsy, but in the spinal cord, the more primitive reticulo-spinal tracts in the lateral columns were noticeably less severely affected than the corticospinal tracts.

Case 2. The Schoolboy.

The findings in this case were consistent with the initial involvement of fibres from Flechsig's areas 42 (angular gyrus) and 41 (medial surface of parietal lobe) with subsequent involvement of those of his areas

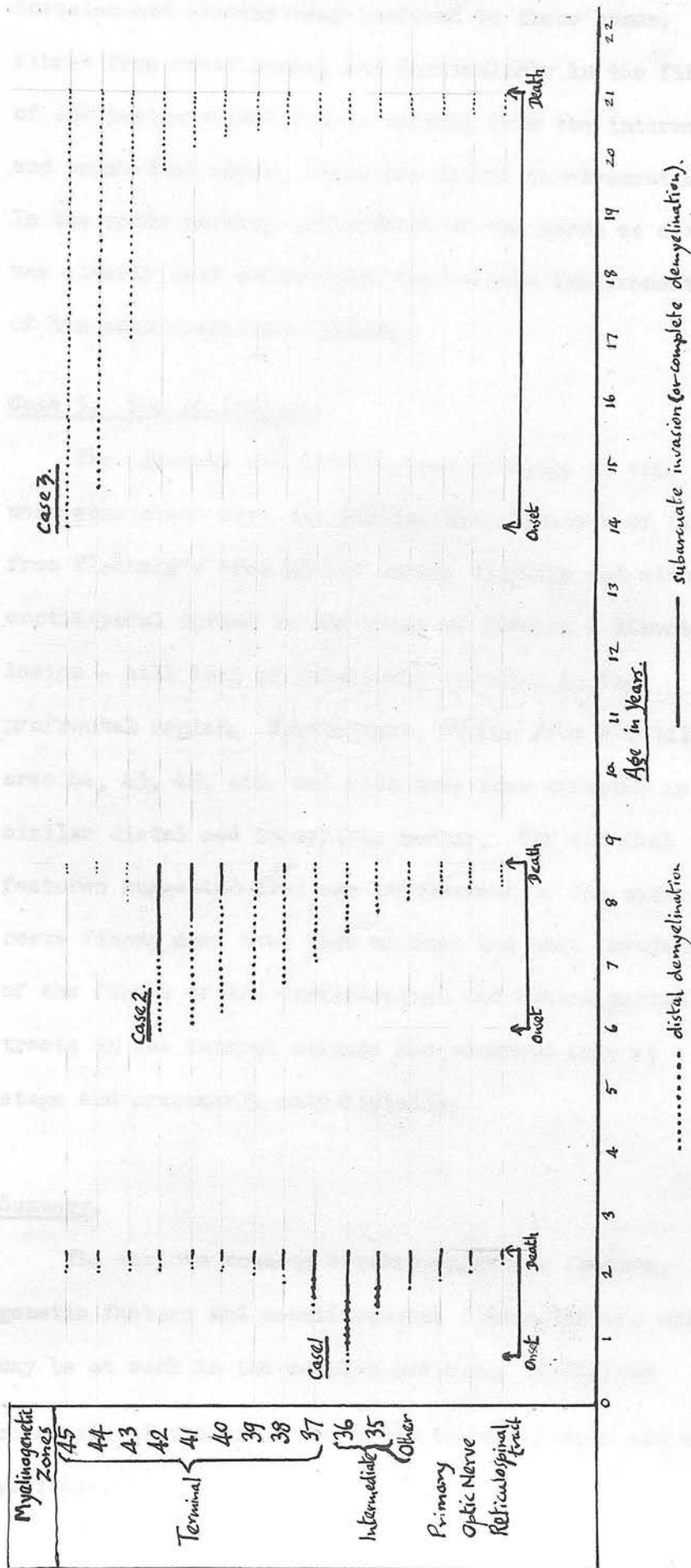


Fig. 54. Possible mode of involvement of the myelinogenetic zones in the three cases reported here.

(insula) and 39 (supramarginal gyrus). Subarcuate invasion had clearly been confined to these zones. In fibres from other zones, and particularly in the fibres of the corticospinal tracts arising from the intermediate and primordial zones, there was distal involvement only. In the optic nerves, involvement of the nerve as a whole was clearly less marked than the obvious involvement of its maculopapillary bundle.

Case 3. The Adolescent.

The clinical and pathological findings in this case were consistent with the initial demyelination of fibres from Flechsig's area 45 but purely distally and without corticopetal spread to the stage of forming a discrete lesion - still less of subarcuate invasion in the prefrontal region. Furthermore, fibres from Flechsig's area 44, 43, 42, etc. may well have been affected in a similar distal and incomplete manner. The clinical features suggested that any involvement of the optic nerve fibres must have been minimal and that involvement of the fibres of the corticospinal and reticulospinal tracts in the lateral columns had occurred only at a late stage and presumably only distally.

Summary.

The various noxious cerebro-exogenous factors, genetic factors and constitutional tissue factors which may be at work in the complex aetiology of diffuse sclerosis of the brain are known to be multiple and widely variable./

variable. Also, there are some general indications that diffuse sclerosis may be pre-eminently and perhaps essentially a disease of the immature brain but the existence of a developmental tissue factor determining the site of onset and subsequent march of the demyelinating process has been generally acknowledged only for the metachromatic leucodystrophic form and, this form has, indeed, been contrasted with the other forms on the ground that the latter show an excentric onset and a variable march which is said not to be a reversal of myelinogenesis. However, this contrast would seem to be based on the assumption that myelinogenesis is a process completed in infancy and that its reversal would, therefore, always take a stereotyped form. An excentric onset and a variable march can indeed be explained on the hypothesis of a developmental predisposition of the white matter provided the prolonged maturation of myelin and the varying topographical pattern of predisposition, according to the age of the individual concerned, are borne in mind. From such a hypothesis, certain tentative but verifiable conclusions about the site of onset of the disease, about the mode of its subsequent spread, about the march of the clinical symptoms and about the final topography of the lesion at autopsy follow. The difficulty of testing such a hypothesis by studying forms of diffuse sclerosis other than the subacute, steadily progressive, kind has, however, always to be borne in mind.

In the three cases of the subacute variety reported here, no specific cerebro-exogenous, genetic or constitutional tissue factors were demonstrated. The existence/

existence of a developmental tissue factor cannot admissibly be firmly deduced from the findings in only three cases but subacute diffuse sclerosis is sufficiently rare, and its detailed clinical study from an early stage so much rarer still, particularly in a group of patients at widely different stages of maturity, as to justify very tentative deductions. With this proviso, the findings in these three cases were such as to support the hypothesis that the specially vulnerable parts of the white matter were those parts which, at the time of onset of the disease, were most actively passing through some specially vulnerable late phase of myelinogenesis mediated by the maturational activity of the interfascicular oligodendroglia and perhaps related to the terminal phases of proteolipid metabolism in the oligodendrocytes.

A NOTE ABOUT CERTAIN OTHER CLINICAL CONDITIONS.

The clinical and anatomical findings in the three cases of subacute diffuse cerebral sclerosis described here raise many questions in relation to other neuro: :psychiatric conditions - particularly in relation to the demyelinating diseases, the postnatal developmental nervous disorders (including infantile autism) and the functional psychoses. It will only be possible, however, to comment very briefly upon some of these questions.

The possibility of a developmental tissue factor in diffuse sclerosis suggests that some of the diversities of manifestation in the demyelinating diseases generally may be explicable in terms of the variable modes of action of an 'exogenous factor' (Einarson, Neel & Strömberg, 1944) upon white matter which is, from infancy up to adult life, passing through a specially vulnerable maturational phase which itself has a wide topographical variability according to age. On this view, the picture of diffuse sclerosis would emerge only with an exogenous factor having a continuously sustained action and quite different clinical and pathological pictures would be expected to emerge with an exogenous factor acting in other modes and at different ages.

In particular, the curious anatomical characteristics of the 'concentric sclerosis' of Baló (1928, 1943), Barré and van Bogaert (1933), and Hallervorden and Spatz (1933) may be understandable from a developmental aspect. The characteristics of that condition have already been the subject/

subject of speculation, the concentric rings of alternating myelination and demyelination having been compared both to ring-spot virus disease and to the Liesegang phenomenon, and have also been the subject of actual experiment. Hallervorden (1952) has suggested the possibility that they may be due to lecithinolytic substances having the faculty of dissolving the myelinated sheath in a specific manner and McAlpine has also carried out experiments which seem to support the latter theory which, therefore, carries a considerable weight of authority. Nevertheless, there are certain features of 'concentric sclerosis' which seem to be inadequately explained by either of these two theories -- in particular the occurrence of parallel bands of myelination and demyelination some of which are not truly 'concentric' but which seem, at least in the illustrations accompanying some of Baló's reports, to run parallel to the cortical grey matter, and of others which appear to run transversely in the corpus callosum. Also, while Baló stated that the obvious 'ring' forms seen on section were concentric spheres he did not conclusively demonstrate this in his reports and, indeed the whole question of the solid geometry of the supposed concentric 'spheres' would require to be studied in relation to that of the nerve fibres involved in order to exclude the possibility that they had, for example, the form of a series of concentric incomplete spheres open in the direction of the nerve fibre groups involved. Now, Baló believed endocrine factors to be of importance in this condition and, relating the findings in one of his cases to the/

the presence of a hypophyseal cyst, he incriminated an abnormal secretion passing up through the hypophyseal stalk into the third ventricle. The plausibility of this explanation is enhanced when the subependymal origin of the oligodendroglia and the phasic nature of endocrine activity in general ^{are} ~~is~~ kept in mind. The abnormal secretion, acting ^{as} an 'exogenous factor', recurring and remitting rhythmically from an early stage of development, and perhaps having the character of an antigen initiating an allergic mechanism, would well help to lay down an oligodendroglial 'insufficiency' (the so-called 'dystrophic tissue factor') having a characteristic topographical pattern. More specifically, oligodendroblasts, migrating from the grey matter into the white in the course of histogenesis, would lay down alternating bands of oligodendroglial normality and 'insufficiency' and thus predetermine the subsequent sites of parallel bands and concentric rings of demyelination.

The picture of multiple sclerosis would emerge if, instead of the sustained exogenous factor of diffuse sclerosis, or the regularly recurring exogenous factor of concentric sclerosis, there were an irregularly intermittent, and briefly sustained, exogenous factor (McAlpine, Compston & Lumsden 1955). Indeed, as Wilson (1940) pointed out, contrasts of diffuse sclerosis with multiple sclerosis are not rendered more substantial by the condition of 'concentric sclerosis' for, from the point of view of the present developmental hypothesis, 'concentric sclerosis' can be regarded as intermediate between/

between diffuse and multiple sclerosis. In the latter condition it would be supposed that the briefly acting intermittent factor would initiate foci of demyelination only at those points in the white matter where the specially vulnerable phase of myelin maturation was taking place. Assuming that the maturation of the white matter of the nervous system takes place as symmetrically as its early, gross, myelination, these foci would, in consequence, be themselves symmetrically placed, both in the brain and in the spinal cord. Subsequent recurrences of the exogenous factor would result in fresh foci being formed at those new sites in the white matter where the vulnerable phase of myelin maturation was taking place, and these, again, would be mainly symmetrically placed. The symmetrical pattern of the focal disturbance is, in fact, a striking feature of multiple sclerosis and one for which no satisfactory explanation has previously been given.

The findings of the present study have less immediate relevance for the aetiology of the developmental nervous disorders of postnatal life or for the functional psychoses. However, the initial dyslexia in the case of the schoolboy raises the question of the non-progressive condition known as 'specific dyslexia' which becomes manifest in otherwise normal and intelligent children at the same age as the patient described. The anatomical basis of the early dyslexia, in the case reported here, in a lesion of the angular gyrus, does seem to lend at least some support to Schilder's (1944) insistence that/

that it is from the neurological point of view that the congenital reading disabilities could, and must be interpreted, rather than to the psychological explanation so strongly emphasised by Kanner (1948) and Mildred Creak (1954).

Finally, the findings in the case of the adolescent raise the question of the significance of diffuse sclerosis for the neuropathology of schizophrenia. The clinical features in this patient were indistinguishable, over a period of several years, from those of schizophrenia and this fact would appear at least to render more plausible the view that schizophrenia is a specifically human disease involving an abiotrophic process affecting the neoecephalic parts of the brain of most recent development - particularly the association areas of the frontal, temporal and parietal lobes and their connections. Actual demyelination and sclerosis are not normally found in the brains of schizophrenics, but abnormalities in the interfascicular oligodendroglia have been repeatedly and constantly observed by Elvidge and Reed (1938) in biopsy studies of material from the brains of schizophrenic patients during life and it is significant that Penfield himself vouched for the validity of this finding. Its significance is hard to assess but it suggests that there may be a relation of the oligodendroglial abnormality in schizophrenia to the oligodendroglial 'insufficiency' which Einarson, Neel & Strömberg (1944) believe to underlie diffuse sclerosis.

Summary.

The findings in the three cases reported here raise many/

many questions in relation to other neuropsychiatric conditions but it is only possible to comment on their relevance for the demyelinating diseases generally, the postnatal developmental disorders and the neuropathology of schizophrenia.

The diversities of manifestation in the demyelinating diseases may be explicable in terms of the variable modes of action of an exogenous factor upon white matter whose vulnerable maturation is spread out over the whole period of childhood and adolescence and whose topographical variability is wide - according to the age of the patient. In particular, the concentric rings of alternating myelination and demyelination in Baló's concentric sclerosis may be explicable on this basis while the developmental tissue factor hypothesis may also explain the hitherto unexplained tendency, in multiple sclerosis, for the lesions to appear in a symmetrical fashion both in the brain and spinal cord.

The findings in the case of the schoolboy seem to lend at least some support to the view expressed by Schilder (1944) that it is from the neurological, rather than from the psychological, point of view that the congenital reading disabilities must be interpreted. The findings in the case of the adolescent tend to support the view that schizophrenia is a specifically human disease involving an abiotrophic process affecting the neocerebral parts of the brain of the most recent development - particularly the association areas of the frontal, temporal and parietal lobes and their connections. They raise, in particular, the question of the possibility of /

of the oligodendroglial abnormalities demonstrable in schizophrenia being related to the oligodendroglial 'insufficiency' in diffuse sclerosis which was postulated by Einarson, Neel & Strömberg (1944).

SUMMARY.

In an introduction, attention was drawn to the special vulnerability of the tissues of bodily organs during the morphogenetic phase of their development, to the especially prolonged morphogenesis of the nervous system and, in particular, to the continued morphogenesis of the cortical mantle of the human brain right up to full adult life. The extent of present ignorance, however, about the role in disease of late maturational processes in the human brain was emphasized, together with the importance of this topic for an adequate understanding not only of the so-called developmental nervous disorders of postnatal life but of the more urgent problem of the functional psychoses. It was pointed out that, while further advances could be expected in the

6. SUMMARY.

neural histogenesis and the corresponding field of behavioral development, advances in the neuropathology of these conditions, which rarely come to autopsy, would probably be delayed. In the light of these observations the unique importance was emphasized of careful clinical and pathological studies, from an earlier stage than heretofore, of the rarer, more serious, diffusely acting, diseases of the still maturing brain. A clinical and pathological study, from the developmental aspect, of three cases of subacute diffuse sclerosis of the brain, occurring at widely different ages and studied clinically from an unusually early stage, was offered as a contribution to this problem.

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In an introduction, attention was drawn to the special vulnerability of the tissues of bodily organs during the morphogenetic phase of their development, to the specially prolonged morphogenesis of the nervous system and, in particular, to the continued morphogenesis of the cortical mantle of the human brain right up to full adult life. The extent of present ignorance, however, about the role in disease of late maturational processes in the human brain was emphasised, together with the importance of this topic for an adequate understanding not only of the so-called developmental nervous disorders of post natal life but of the more urgent problem of the functional psychoses. It was pointed out that, while further advances could be expected in the field of post natal cerebral histogenesis and the corresponding field of behavioural development, advances in the neuropathology of these conditions, which rarely come to autopsy, would probably be delayed. In the light of these observations the unique importance was emphasised of careful clinical and pathological studies, from an earlier stage than heretofore, of the rarer, more serious, diffusely acting, diseases of the still maturing brain. A clinical and pathological study, from the developmental aspect, of three cases of subacute diffuse sclerosis of the brain, occurring at widely different ages and studied clinically from an unusually early stage, was offered as a contribution to this problem.

In this study, an outline was first given of present knowledge about postnatal growth and maturation of the human/

human brain during infancy, childhood and adolescence and of the behavioural development which it subserves, with special reference to the maturation of the cerebral white matter and its oligodendroglia. This was followed by full clinical and pathological accounts of the three original cases of subacute diffuse sclerosis. Then, in the light of the actual findings, the role of a developmental, myelinogenetic, tissue factor in subacute diffuse sclerosis was discussed and certain general conclusions drawn. In this discussion, a historical survey first outlined the development of interest in diffuse sclerosis and in particular drew attention to references in the literature which could be interpreted as suggesting that the onset of the disease might have a relationship to some terminal and peculiarly vulnerable stage in the maturation of myelin in the brain. Then, from the clinical aspect, it was pointed out that early symptoms though variable and inadequately studied, seemed to have a certain specificity for age of onset and that, more particularly, in the three cases described, it had been deterioration of the behavioural characteristic of the individual most actively maturing at the time which had constituted the initial disturbance. In the infant this had taken the form of a progressive failure, from the age of nine months, to learn to stand erect and to walk unaided, in the young schoolboy it had taken the form of a failure, from the age of six years, to complete the process of learning to read and in the case of the adolescent it had taken the form of failure, from the age/

age of thirteen or fourteen years, to complete the emotional, intellectual and social maturation characteristic of that epoch. From the pathological aspect, the actual findings were found to be consistent with, and in certain particulars to confirm, in the light of present knowledge of the anatomical basis of these capacities, anatomical deductions from the clinical observations. From the aetiological aspect, little light was thrown upon specific cerebro-exogenous, genetic or constitutional tissue factors in the particular cases and, with regard to the possibility of a developmental tissue factor, the inadmissibility of drawing definite conclusions from the findings in only three cases was acknowledged. However, the rarity of diffuse sclerosis, and still more of its detailed clinical study from an early stage in patients of widely different ages, was pleaded as a valid reason for the argument that the findings suggested, and certainly were consistent with, the tentative hypothesis that the initial demyelination had taken place in regions of the white matter where some terminal phase in myelin maturation, possibly related to the metabolism of the neurokeratin proteolipids, had been most actively taking place.

Certain even more tentative suggestions were finally put forward about an analogous developmental tissue factor in the demyelinating diseases generally, particularly in the concentric sclerosis of Baló and in multiple sclerosis. In particular, it was suggested that the hitherto unexplained tendency, in multiple sclerosis, to the formation of symmetrical lesions, could be explained on/

on the basis of such a factor. Finally, there was brief reference to possible histogenetic factors in the development of mental nervous disorders, especially specific developmental dyslexia, and in the functional psychoses, particularly schizophrenia.

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A DEVELOPMENTAL FACTOR IN SCHILDER'S DISEASE

BY

JAMES F. McHARG